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ERRATA

Physical Measurements of Diabetic Patients. Root and Miles. *J. Metabol. Research*, 2, 1922, p. 173.

Page 177. Table I. 3rd line from bottom. "Actul." should be "Actu.1".

Page 178. Table II. 3rd line from bottom. "Actul." should be "Actu.1".

Page 187. Second paragraph, second line. Omit the repetition of "are found also in glucose tolerance but".

Page 197. Reference 2. 1921 should be 1912.

A Modified Haldane Open Circuit Apparatus for Measuring the Respiratory Exchange in New Born Babies and Also in Rabbits and Cats. Marine. *J. Metabol. Research*, 2, 1922, p. 29.

Page 36. Table IX should be omitted. It properly belongs with the paper of Pemberton in Vol. 2, No. 3.

The Influence of Benzyl Benzoate Upon Nitrogenous Metabolism. Pack and Underhill. *J. Metabol. Research*, 2, 1922, p. 73.

Page, 76, line 9. Should read "lysis, it is very probable that the therapeutic effects would be".

Page 104, conclusion (5). Should read "Sodium benzoate is the most toxic of the preparations employed."

Quantitative and Qualitative Changes in the Islands of Langerhans in Diabetes Mellitus. Conroy. *J. Metabol. Research*, 2, 1922, p. 367.

Page 372. Figure oposite Case No. 1 under the heading "Average No. of normal isles per section" should be 68.9 instead of 62.2. Figure opposite Case No. 10 under the heading "Total No. of isles in sections" should be 368 instead of 386.

Page 373. Figure opposite Case No. 7 under the heading "Average No. of normal isles per section" should he 193.1 instead of 191.3.

Page 376. Second paragraph, ninth line. Should read "95. Including one case of hemochromatosis, in which the findings are discussed separately, there are altogether 120 cases with 12 diabetics and 107 controls."

Influence of Glands with Internal Secretion on the Respiratory Exchange: VII. The possible Influence of Suprarenal Involution in New Born Infants on Heat Production. Marine, Lowe and Cipra. *J. Metabol. Research*, 2, 1922, p. 329.

Page 332, line 18. Should read "were in the hospital. In three instances the babies could not remain in the hospital throughout", etc.

Page 337, line 4. Should read "1 — 7 days" instead of "1 — 1 days".

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INFLUENCE OF GLANDS WITH INTERNAL SECRETIONS ON THE RESPIRATORY EXCHANGE.

VI. Further Data on the Effect of Suprarenal Insufficiency (by Removal) in Rabbits.

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In an earlier paper[1] it was shown that partial but sufficient destruction of the suprarenal cortex, in rabbits with intact thyroids, caused a prolonged rise in heat production. This reaction was obtained in 40% of all rabbits (15) in which partial destruction of the suprarenal function was attempted by freezing and in 74% of all rabbits (38) in which partial destruction of the suprarenal function was attempted by removal.

In the rabbit, the function of the suprarenal gland may usually be sufficiently crippled by total removal of the main glands or by severe freezing. This is, of course, dependent upon the presence of accessory cortical tissue. In the dog and cat total removal of the main glands cannot be utilized because of the rarity of accessory suprarenal cortical tissue, and because approximately 90% die within five days after this operation however excellent the surgical technique and after-care may have been. Many investigators have attempted to produce a severe but sublethal injury to the suprarenal function by partial removal[2]. These attempts have in most instances resulted in failure because of the uncontrollable nature of such procedures. Either too much or too little of the suprarenal function has been supressed. For similar reasons attempts to peel off the cortex or to curette out the medulla[3] may be dismissed from consideration. We concur with the views of those investigators who believe that from the physiological point of view more than 90% of dogs and cats with double suprarenalectomy may be regarded as dying from the time of double suprarenalectomy.

Numerous investigators[4 5 6 7] have studied the temperature, blood pressure and various phases of metabolism in cats and dogs after total supression of the suprarenal function. All workers are substantially in agreement regarding the effects produced, namely, a fall in temperature, in blood pressure and in metabolism, setting in usually within a few hours and continuing to death. The most recent confirmation of these effects, especially as regards metabolism, have been reported by Aub, Forman and Bright[8] on cats.

Many of the older investigators, realizing the limitations of experiments terminating so quickly in death attempted to induce sublethal injury or at least a more gradual fatal termination. Hoskins[9] in his blood pressure studies accomplished this end by partial removal and by vessel ligation. Golyakowski[10] in 1899 in his studies in heat production in dogs produced a partial suppression of the suprarenal function by vessel ligation. He performed ligations of the suprarenal veins in twelve dogs. Three of these died within three days; one survived twenty-eight days, and eight lived longer than six weeks. He measured the respiratory exchange in these dogs and found in those surviving longer than six weeks a striking increase in heat production. Hartmann and Blatz[11] also utilized the method of vessel ligation in their studies on the chronic effects of sublethal insufficiency in cats. As is well known, vein ligation is often rapidly fatal both in dogs and cats.

Marine and Lenhart[12] and Marine and Baumann[1] attempted to further eliminate the dangers of a rapidly fatal outcome following suprarenalectomy by using rabbits. On account of the almost constant presence of accessory suprarenal cortical tissue in this animal, it has been found possible to obtain, easily, a gradated series of suprarenal insufficiencies from the rapidly fatal to the non-fatal, merely by complete removal or by severely freezing the main suprarenal glands. Extensive experimental work has shown that reactions with increased heat production following double suprarenalectomy in rabbits can be produced in as high as 82% of a total of 33 rabbits, while with freezing in this animal we have obtained a rise in only 40% of a total of 15 rabbits. More recently Scott[13] working in this Laboratory has shown that similar rises in heat production can be obtained in cats by sublethal injury to the func-

tion of the suprarenals either by vein ligation or by freezing but rarely by partial or total removal.

In any large series of animals whether dogs, cats or rabbits, the types of reaction following severe injury to the suprarenals by the above mentioned methods fall roughly into three groups, as follows: (See Table VI).

Group 1. Those that survive indefinitely after removal or injury of the suprarenals with no appreciable alteration in the respiratory exchange or clinical behavior.

Group 2. Those that show a gradual rise in the respiratory exchange followed by a gradual fall to or below the normal level whether dying within two or three weeks or living on indefinitely.

Group 3. Those that show a fall (sometimes rapid, sometimes gradual) in the respiratory exchange and continuing to death.

Group 1 represents those animals in which the suprarenal injury was too slight and Group 3 represents those in which the severity of the injury overwhelms the animal and prevents the reaction of increased heat production. This latter phenomenon is doubtless similar physiologically to the absence of febrile reactions or of leucocytoses in certain profound bacterial intoxications. The proportion of experiments falling in each of these groups necessarily varies with the animal used. With dogs and cats a relatively large proportion would fall into Group 3 irrespective of the means used in crippling the suprarenal function, while with rats a relatively large proportion would fall into Group 1. There is no doubt that much of the confusion and many of the contradictory results of experiments involving extirpation of the suprarenals have been dependent upon differences in the skill and experience of the investigators[14]. In the relatively simple procedure of extirpation extraordinary differences in the duration of life have been recorded by different investigators using the same species of animals. It is not surprising therefore that highly technical experiments based on partial or complete extirpation of the suprarenals as a starting point should show still greater variations.

The purpose of this paper is to present eleven additional experiments on rabbits again showing that sufficient crippling of the suprarenal function with intact and iodin containing

thyroids usually causes a reaction with increased heat production. The following four protocols have been selected to show in detail the data obtained and to illustrate the three major groups of heat production reactions above mentioned.

GROUP I.

Protocol 1. Rabbit 252.* Female — gray adult.

Feb. 13, 1921. Began metabolic studies.

Mch. 14. Under ether exposed and froze R suprarenal with ethyl chloride. The gland has a long attachment to inferior cava and probably the portion facing the inferior cava was not frozen. Also isolated and froze completely the L suprarenal including its vessels and nerves. Both suprarenals enlarged.

Mch. 16. Rabbit has shown no ill effects of operation, active, eats full ration.

Apr. 1. Rabbit apparently in perfect health.

Sept. 1. Animal has remained in excellent condition. Transferred for antibody work.

Sept. 21. Under ether removed most of R and L thyroid lobes.

Dec. 30. Killed. Apparently in good condition, except striking evidence of myxedema, fur dry and thin, skin thickened. Both thyroid lobes absent, no fragments or accessory thyroids found on careful search. No thymus tissue visible. Lungs and heart normal; liver and spleen normal. L suprarenal normal in size and color; microscopically, marked hypertrophy of cortical cells compressing area of atrophic cortical tissue filled with cholesterol spaces (remains of injury from freezing); one 2 mm. accessory above and external to the L suprarenal and 2 other large accessories on external surface of L kidney. R suprarenal is reduced in size, measuring 4 x 3 mm., of a yellowish brown color, soft; microscopically, only atrophic cortical

TABLE I. *Rabbit 252.*

DATE	Room Temperature	Weight of Rabbit	O_2 in grams, 2 hours	CO_2 in grams, 2 hours	R. Q.	Total Calories 2 hours	Calories per kgm. per hour	Behavior of Animal
1921		Grams						
Feb. 15	24.9	2542	4.070	4.650	83	13.80	2.71	Very restless
" 24	21.2	2669	3.750	4.345	84	12.77	2.39	Quiet
Mch. 4	19.4	2683	4.280	5.655	96	14.99	2.79	*Very* restless
" 16	21.8	2833	4.220	5.975	103	15.35	2.71	Quiet
" 18	20.6	2865	4.460	5.740	94	15.46	2.70	Restless
" 21	23.2	2930	4.200	5.615	97	14.76	2.52	Quiet
" 23	23.2	2850	3.605	4.780	96	12.67	2.22	"
" 25	21.8	2820	4.205	5.390	93	14.63	2.59	Restless
" 31	23.6	2864	4.025	5.055	91	13.96	2.44	Quiet
Apr. 4	22.0	2922	4.235	5.165	89	14.51	2.48	"

Mch. 14. R and L suprarenal frozen

* Chosen from a former series as no typical example of Group I occurred in the experiments included in this paper.

cells with numerous cholesterol spaces present. Kidneys normal in appearance; stomach normal; abundant fat in all depositories.

GROUP II.

Protocol 2. Rabbit 261. Male — young adult.

Apr. 2, 1921. Began metabolic studies.

Apr. 28. Under ether removed R and L suprarenal glands completely, through usual R and L lumbar incisions. R suprarenal weight 0.2 gm. and L suprarenal weight 0.25 gm.

Apr. 29. Eating ration, possibly a bit dull.

May 1. Eating heartily.

May 7. Very dull, weak, looks like rapidly developing suprarenal insufficiency, gave glucose by mouth.

May 11. Still very weak eating carrot and lettuce.

May 14. Very active, eating oats and hay.

May 17. Active, nervous, becoming vicious, bites at hand for first time; sexually active.

May 18. Rectal temperature 101.6 F.

May 20. Blood urea 18.9 mgm.; creatin 1.7 mgm.

Jun. 11. Active and hearty.

Jul. 10. Dull but restless, eating very little, very weak.

Jul. 14. Much improved, active but tires easily.

Aug. 16. The two hour period in metabolism chamber made him very weak. Ears slightly cyanotic, slight dyspnea as if cardiac weakness.

Aug. 17. Still weak and dyspneic. This was the worst of several dyspneic periods during the last two months. Looks like cardiac weakness.

Sept. 3. Another period of cardiac weakness began after slight handling.

Sept. 4. Very weak, dyspneic and unable to stand. Killed and autopsied at once. Weight 1733 gm. Thyroid lobes are very hyperemic, possibly slightly enlarged; paras normal; thymus present, but reduced in amount. Lungs normal; heart dilated, very flaccid. Spleen small; stomach contains moderate amount of food, mucosa shows recent and old ecchymoses in pyloric portion; pancreas hyperemic. Liver gray-brown flaccid and tougher than normal. Both kidneys yellowish gray in color, no pitting and not reduced in size. R and L suprarenals completely removed; two very small 1 mm. accessory suprarenals found on inferior cava. Lymph glands not enlarged; testes small and soft; moderate abdominal fat.

Rabbit 261.

TABLE II.

DATE	Room Temperature	Weight of Rabbit	O_2 in grams, 2 hours.	CO_2 in grams, 2 hours.	R. Q.	Total Calories, 2 hours.	Calories per kgm. per hour.	Behavior of Animal
1921		Grams.						
Apr. 15	21.0	1862	2.365	3.030	93	8.23	2.21	Quiet
" 21	22.4	1864	2.265	2.905	93	7.89	2.12	Restless
" 29	22.0	1820	2.555	2.940	84	8.64	2.37	"
" 30	25.5	1820	2.620	3.400	94	9.16	2.52	Quiet
May 2	21.9	1812	2.440	3.455	97	9.08	2.51	"
" 5	24.0	1773	2.520	3.330	96	8.82	2.49	"
" 7	23.1	1646	2.440	2.745	82	8.22	2.50	Very dull
" 9	19.6	1607	2.780	3.050	80	9.32	2.90	*Very* "
" 10	21.4	1583	2.065	2.420	85	7.05	2.23	Restless
" 12	24.0	1587	2.090	2.600	90	7.24	2.28	Dull
" 16	23.4	1828	3.180	4.525	103	11.62	3.18	Very dull
" 18	23.0	1836	3.520	4.685	97	12.32	3.35	Dull
" 26	22.1	1807	3.695	4.435	87	12.68	3.51	Quiet
" 23	25.1	1747	2.950	3.800	94	10.23	2.93	"
" 24	24.3	1813	2.955	4.320	106	11.10	3.06	"
" 26	22.4	1853	3.220	4.245	96	11.25	3.04	"
" 28	23.3	1793	3.165	3.985	92	10.91	3.04	"
" 31	23.4	1802	2.780	3.580	94	9.64	2.68	"
June 4	23.8	1809	2.960	3.670	90	10.22	2.83	"
" 8	23.5	1771	2.830	3.500	90	9.75	2.75	"
" 11	25.2	1771	2.830	3.440	88	9.75	2.75	"
" 15	24.5	1750	3.015	3.390	82	10.16	2.90	"
" 21	25.0	1747	2.725	3.475	93	9.43	2.70	"
" 29	28.7	1818	2.965	3.550	87	10.15	2.78	"
July 7	27.8	1751	2.685	3.710	100	9.53	2.72	"
" 13	26.2	1699	2.860	3.490	89	9.81	2.89	Slightly restless
" 19	27.4	1748	3.350	3.620	79	11.17	3.20	Rapid resp.
" 22	25.8	1758	2.445	3.285	98	8.50	2.44	" "
" 28	30.8	1747	2.965	3.555	87	10.17	2.91	Slightly restless
Aug. 1	24.1	1725	2.790	3.385	88	9.60	2.78	Quiet
" 10	25.6	1729	2.780	3.550	93	9.64	2.80	Very quiet
" 16	24.8	1808	2.675	3.170	86	9.15	2.53	Quiet
" 23	24.4	1796	2.790	3.440	90	9.58	2.67	Very dull
" 30	25.7	1807	2.975	3.410	83	10.12	2.80	Quiet
Sept. 3	28.0	1766	1.450	1.400	70	4.77	2.70	*Mkd. asthenia*

Apr. 28 R and L suprarenalectomy

Protocol 3. Rabbit 293. Male — young gray adult.

Nov. 28, 1921. Began metabolic studies.

Nov. 30. Under ether removed R suprarenal complete, very small, weight 0.13 gm.

Jan. 4, 1922. Under ether removal L suprarenal complete, weight 0.21 gm. Kidneys normal and abdominal fat abundant.

Jan. 9. Skin stitches tore out, probably in handling, resutured.

Jan. 21. Soft stools; eating well.

Meh. 25. Used for antibody work.

Jul. 8. Under ether removed R and L testes, normal size, a 2 mm. accessory found in each spermatic cord near the testis.

Jul. 13. Has shown no ill effects from gonadectomy. Weight 2341 gm. Killed and autopsied at once. Gonadectomy wound healed. Thyroid lobes not enlarged very hyperemic; paras pale and small; thymus large and cellular; heart in systole, appears normal. Very small patches of consolidation in both upper lobes of lungs. R and L suprarenals absent, sites clean. One 2 mm. accessory on L side above site of L suprarenal. Liver and spleen normal; pancreas hyperemic; kidneys show slight pittings; stomach filled with food, mucosa intact. Testes absent. Very little abdominal fat.

TABLE III.

Rabbit 293

DATE	Room Temperature	Weight of Rabbit	O_2 in grams, 2 hours.	CO_2 in grams, 2 hours.	R. Q.	Total Calories, 2 hours.	Calories per kgm. per hour.	Behavior of Animal
1921								
Dec. 2	24.5	2486	4.390	5.150	85	15.00	3.02	Rapid resp.* — Quiet
" 5	23.2	2486	4.220	5.370	93	14.58	2.93	" " "
" 7	21.8	2472	4.430	5.080	83	15.07	3.05	" " "
" 8	23.0	2428	3.900	4.450	83	13.20	2.72	" " "
" 10	23.0	2468	3.840	4.510	85	13.13	2.66	" " "
" 13	23.5	2473	3.820	4.650	89	13.07	2.64	" " "
" 16	25.0	2445	4.040	4.750	86	13.71	2.80	" " Very "
" 21	22.0	2484	3.850	4.910	93	13.33	2.68	" " "
" 30	23.0	2472	3.770	4.720	91	13.03	2.64	Quiet
1922								
Jan. 3	22.5	2466	3.780	4.400	85	12.81	2.60	"
" 6	21.5	2413	3.490	4.460	93	12.11	2.51	" Rapid resp.
" 9	23.0	2389	4.130	4.620	81	13.98	2.92	"
" 12	20.2	2300	3.500	3.890	81	11.77	2.56	"
" 16	21.0	2295	4.030	4.540	82	13.60	2.96	"
" 19	24.5	2312	3.870	4.540	85	13.22	2.86	"
" 24	20.5	2363	3.860	4.510	85	13.13	2.78	"
" 27	23.8	2416	3.680	4.570	90	12.72	2.63	"
" 31	22.5	2463	4.400	4.960	82	14.86	3.02	"
Feb. 3	21.4	2488	4.330	5.310	89	14.92	3.00	"
" 6	22.0	2484	4.610	5.100	80	15.58	3.14	"
" 9	22.0	2495	5.380	5.860	79	18.08	3.62	"
" 13	22.8	2481	4.420	4.920	81	14.88	3.00	"
" 16	18.0	2466	4.050	4.770	86	13.77	2.79	"
" 20	23.4	2472	4.360	4.890	82	14.65	2.96	"
" 23	23.4	2497	4.630	5.040	79	15.53	3.11	"
" 27	22.8	2486	3.950	5.120	94	13.79	2.77	"
Mch. 2	24.4	2488	5.150	5.060	72	17.02	3.42	"
" 6	22.6	2478	5.090	5.500	79	16.97	3.43	"
" 9	23.6	2528	5.160	5.510	78	17.17	3.40	"
" 13	22.0	2528	4.640	5.050	79	15.58	3.08	"
" 16	18.2	2510	4.500	4.970	80	15.18	3.02	"
" 20	20.8	2503	4.200	4.620	80	14.11	2.82	"
" 23	23.8	2528	5.050	5.450	78	16.99	3.36	"
" 27	23.5	2458	4.750	4.770	73	15.68	3.19	"
" 30	24.0	2482	5.340	5.360	73	17.62	3.55	"
Apr. 3	23.0	2433	4.710	5.010	77	15.78	3.24	"
" 6	21.0	2503	4.200	4.870	84	14.31	2.86	"
" 10	22.5	2514	4.210	4.800	83	14.24	2.83	"
" 13	23.8	2525	4.610	5.250	83	15.58	3.08	"
" 17	24.2	2508	3.910	4.570	85	13.31	2.65	"
" 20	22.5	2503	3.940	4.320	80	13.20	2.64	"
May 8	21.0	2505	4.000	4.680	85	13.63	2.72	"
" 16	21.2	2508	4.200	4.520	78	14.09	2.81	"

* This rabbit's respiration was always rapid.

Nov. 30 R suprarenalectomy
Jan. 4 L suprarenalectomy

GROUP III.

Protocol 4. Rabbit 307. Female — white adult.

Dec. 13, 1921. Began metabolic studies.

Jan. 13, 1922. Gave birth to 5 young.

Jan. 31. Under ether removed R suprarenal, weight 0.17 gm. Abundant abdominal fat. Kidneys normal.

Mch. 7. Under ether removed L suprarenal completely, weight 0.25 gm.

Mch. 17. Gave 25 mgm. KI by mouth.

Mch. 28. Dull, eats only cabbage and lettuce; severe snuffles with nasal discharge; slowly getting weaker.

Mch. 30. Gave 7cc. ox suprarenal cortex emulsion by mouth.

Mch. 31. Gave 7cc. ox suprarenal cortex emulsion by mouth.

Apr. 1. Gave 12cc. ox suprarenal cortex emulsion by mouth; not eating, weaker.

Apr. 3. Died 1 hour after being run for metabolism. Autopsy at once. Thyroid lobes pale, translucent, yellow (iodized), paras normal; thymus atrophic; heart dilated, flaccid; lungs normal; no arteriosclerosis; liver dark red, about ½ normal size; kidneys small, no pitting; pancreas and spleen normal; ovaries bright yellow, perhaps slightly enlarged; stomach nearly empty, one large nearly healed ulcer in pyloric region and many small recent erosions. Moderate amount of abdominal fat. Death due to progressive suprarenal insufficiency.

TABLE IV.

Rabbit 307

DATE	Room Temperature	Weight of Rabbit Grams.	O_2 in grams, 2 hours.	CO_2 in grams, 2 hours.	R. Q.	Total Calories, 2 hours.	Calories per kgm. per hour.	Behavior of Animal
1921								
Dec. 13	23.5	2301	3.570	4.290	87	12.27	2.67	Quiet
" 15	22.4	2289	3.490	4.100	85	11.94	2.61	"
" 20	22.0	2371	3.530	4.430	91	12.23	2.58	"
1922								
Jan. 11	22.5	2512	3.950	4.320	80	13.20	2.63	"
" 19	24.5	2353	3.740	4.380	85	12.75	2.68	Rapid resp
" 26	21.6	2333	3.450	4.120	87	11.78	2.53	Quiet
" 30	22.2	2312	3.140	4.090	95	10.92	2.36	"
Feb. 2	23.0	2368	3.570	4.580	93	12.43	2.63	Restless
" 6	22.0	2367	3.570	4.550	93	12.35	2.61	Quiet
" 9	22.0	2347	3.480	4.190	88	11.88	2.53	"
" 13	22.8	2409	3.300	4.460	98	11.64	2.42	"
" 16	18.0	2392	3.520	4.150	86	11.98	2.50	"
" 20	23.4	2382	3.220	4.010	91	11.07	2.32	"
" 23	23.4	2402	3.670	4.560	90	12.69	2.64	"
" 27	22.8	2372	3.270	3.830	86	10.95	2.31	"
Mch. 6	23.0	2399	3.600	4.040	82	12.10	2.52	"
" 9	23.6	2340	3.170	3.880	89	10.90	2.33	"
" 11	20.2	2371	3.280	4.400	98	11.48	2.42	"
" 13	22.0	2296	3.280	4.090	91	11.29	2.46	"
" 16	18.2	2242	3.310	3.910	86	11.28	2.52	"
" 20	20.8	2185	3.020	3.480	84	10.23	2.34	"
" 27	23.0	2119	3.080	3.560	84	10.46	2.46	"
" 30	23.0	2022	2.760	2.950	78	9.20	2.27	"
Apr. 3	23.0	1835	2.240	2.560	83	7.60	2.07	"

Jan. 31, 1921 R suprarenalectomy
Mch. 7 L suprarenalectomy
Mch. 17—25 mgm. KI

In addition to the four protocols published in detail, the general data bearing on the subject under discussion obtained from the entire series of eleven experiments have been summarized in Table V.

Rabbit No. Sex	Interval between removal of 1st and 2nd Suprarenal	Duration of life after removal of 2nd Suprarenal	Average normal metabolism Calories per kg. per hour	Average metabolism after Suprarenalectomy in calories per kg. per hour.					Duration of period of increased metabolism.	Fragments or Accessory Suprarenals	Thyroid Histology	REMARKS
				1—14 days	15—28 days	29—42 days	43—56 days	71—84 days				
	days	days							weeks			
261 m.	0	Died 129	2.14	2.48	3.18	2.82	2.78	3.05	17	2—1 mm. accessories on inferior cava.	Slight hyperplasia colloid reduced.	
263 f.	12	Died 81	2.20		2.57	2.63	2.79		11	2—minute accessories on inferior cava. 1—0.5 mm. on R kidney.	Moderate hyperplasia hyperaemia, reduced colloid.	25 mgm. KI given 24 days after removal of 2nd suprarenal and 67 days before death.
264 m.	12	Died 120	2.02		2.94	3.20	3.12	2.93	17	1—2 mm. and 1—1 mm. accessories on R and L epididymis.	Mod.- marked hyperplasia no visible colloid.	25 mgm. KI given 24 days after removal of 2nd suprarenal and 96 days before death.
274 m.	50	Died 36	2.14	2.49	2.30	2.09			5	1—1 mm. accessory on L kidney.	Large distended follicles scattered throughout. Early active hyperplasia.	25 mgm. KI given 54 days before removal of 2nd suprarenal and 90 days before deatb.
275 m.	23	Indef. Killed 191	2.38	2.71	2.57	2.44	2.38		8	1—1 mm. accessory on L epididymis; 1—2 x 3 mm. accessory in R epididymis.	Moderate hyperplasia.	25 mgm. KI given 27 days before removal of 2nd suprarenal and 218 days before death.
289 m.	12	Died 199	2.86		3.36	3.21	3.01		11	2—2 mm. accessories on L epididymis.	Colloid-quiescent (KI) evidence of previous active hyperplasia.	25 mgm. KI given 24 and 138 days after removal of 2nd suprarenal and 218 days before death.
293 m.	35	Indef. Killed 190	2.68	2.74	2.82	3.19	2.91	3.10	23	1—2 mm. Accessory above L adrenal site. 4—1 mm. Accessories in Epididymis.	Eearly hyperplasia lymphoid infiltration	75 mgm. KI given 27 days before removal of 2nd suprarenal and 217 days before death.
294 m.	35	Died 115	2.69	2.82	3.35	3.24	3.06	3.22	14	1—3 mm. and 1—1 mm. accessory on R epididymis.	Colloid-quiescent (KI) evidence of previous hyperplasia.	50 mgm. KI given 27 days before removal of 2nd suprarenal and 142 days before death.
304 f.	0	Died 33	2.63	2.57	2.58	2.50			0	None found.	Mkdly iodized — colloid.	25 mgm. KI given 26 days after removal of 2nd suprarenal and 7 days before death.
307 f.	35	Died 27	2.58	2.41	2.27				0	None found.	Mkdly iodized — colloid.	25 mgm. KI given 10 days after removal of 2nd suprarenal. Last dose 3 days before death.
309 f.	35	died 17	2.56	2.82	2.97				2-½	0.3 mm. accessory near site of L suprarenal.	Mkdly iodized — colloid.	25 mgm. KI given 10 days after removal of 2nd suprarenal and 7 days before death.

In this series of experiments, suprarenal insufficiency was attempted by the method of gland extirpation. Careful necropsies showed that both main suprarenal glands had been completely removed in all cases. In two experiments both suprarenal glands were removed at a single operation, while in the remaining nine, from twelve to fifty days intervened.

Accessory suprarenal tissue was demonstrated at autopsy and checked microscopically in nine cases. The failure to demonstrate accessory tissue in two, at least indicates it was present in very small amounts. Further proof of a serious suprarenal deficiency in these two cases is afforded by the fact that they were the only ones which showed a progressive fall in heat production to death — that is the only two instances of Group 3. Analysing the data of accessory suprarenal tissue further they support the views expressed by other recent investigators and by our own previous reports, that the duration of life after suprarenalectomy depends on the amount of functionally active accessory cortex remaining. Thus, the largest amount of accessory tissue was found in the two that survived indefinitely in excellent condition, while the least was found in those (3) that survived the shortest period of time. A similar relation of the amount of accessory cortex to the duration of life is also seen in the remaining experiments of this series. It will be noted that the length of life after double suprarenalectomy was greater than the average reported by many other investigators. We have pointed this out for other series of similar experiments as well. The data relative to accessory cortical tissue and to the duration of life of our entire series (now about 300) of rabbits during the last seven years in which both suprarenals were completely removed will be published separately. It suffices here to state that there is a sufficiently close relationship between the amount of accessory suprarenal cortex found at autopsy and the duration of life to justify the conclusion that the cortex is the portion of the suprarenal which determines survival or death.

Classifying the eleven experiments according to their heat production reactions, it is seen that there is no example of Group 1; that nine (82%) fall in Group 2, and two in Group 3. These proportions are due to the fact that insufficiency was induced by extirpation rather than by freezing or by partial

removal. (See Table VI). In other words, total extirpation of the main suprarenal glands in the rabbit has been the most

TABLE VI.

Nature and Degree of Injury to Suprarenal Glands	Group I No rise in Heat Production		Group II Rise in Heat Production		Group III Fall in Heat Production	
		%		%		%
Frozen	8	53	6	40	1	7
Complete removal	2	6	27	82	4	12
Incomplete removal	4	80	1	20	0	--
Totals	14	26	34	64	5	9

certain means of producing the optimum suppression of suprarenal function to demonstrate increased thermogenesis.

Duration of the rise in heat production. — As pointed out in a previous paper this is highly variable. In our experiments with rabbits it occasionally lasts only a few days but most frequently for a few weeks and rarely for several months. The longest period of increased metabolism studied was twenty-three weeks (see Rabbit 293) with the usual periods of exacerbation and remission.

The rise in heat production occasionally is demonstrable within twenty-four hours after removal of the second suprarenal, but more frequently begins in from three to six days. There may be a fall in heat production during the first twenty-four to forty-eight hours after the operation of bilateral extirpation. This, we believe, is due to the "shock" of the operation.

The heat production reaction after suprarenal injury with intact thyroids is a natural physiological response. If too little injury is done heat production remains unchanged. If the injury is too severe there is a fall to death. These types of reactions are illustrated graphically in the charts (see Figures 1, 2, 3 and 4). The chart for Rabbit 252 shows the reaction after too slight an injury to the suprarenals, i.e. no change in heat production. The chart of Rabbit 307 illustrates the fall in heat production which results from too severe an injury to the suprarenals. The charts of Rabbits 261 and 293 illustrate the usual reaction in heat production following suprarenal

extirpation. The maximum percentile rises in heat production after suprarenalectomy were 71% in Rabbit 264 and 62% in Rabbit 261. This increase in heat production is absolute as shown by the CO_2 and O_2 figures.

The histological condition of the thyroid is of interest when taken in relation with the administration of iodin. Great care has been exercised to prevent the uncontrollable contact of the animals with iodin. The necessity for this in all work involving thyroid function has been emphasized many times. The amounts of iodin (KI) administered and its time relation to suprarenalectomy and to the duration of life are indicated in Table V. In the first place, suprarenalectomy does not impair the ability of the thyroid to store iodin. This is important. Secondly, there is a more rapid loss of iodin from the thyroid following sufficient suprarenal injury than occurs in control animals. This is indicated by the more rapid hyperplasia of the thyroid but has also been demonstrated by iodin determinations on both cats and rabbits.

Discussion.

There can be no doubt that sufficient injury to the function of the suprarenal glands in both rabbits and cats leads to an increase in heat production, provided the thyroid is intact and discharging its iodin containing hormone. This has now been demonstrated in a large series of rabbits and cats. If the injury is too severe, a fall in heat production occurs and if the injury is too slight no change is obtained.

There is likewise no doubt that removal of the thyroid gland prevents the increased heat production. This reaction, therefore, is in part dependent on an increased discharge of the iodin-containing hormone from the thyroid. The mechanism of this increased discharge is still unknown but it is believed to depend upon a loss of the regulatory control normally exercised by the suprarenal cortex.

Aub and his collaborators reported a small series of cats in which they failed to obtain the increased heat production. Their failure, we believe, was due to the methods used. They attempted to produce suprarenal insufficiency by complete and by partial removal of the glands. All investigators agree that total suppression of suprarenal function in cats or dogs leads to a rapidly fatal termination with a fall in heat

production. Aub was unable, and we have likewise been unable to produce increased heat production by partial removal in cats. In a very large series of partial removals an accidentally successful instance would probably occur. Owing to the narrow anatomical and physiological limits within which one has to work, usually either too much or too little of the suprarenal function is destroyed by this method. Scott[13] has been able by the method of freezing and vessel ligation, separate and combined with partial removal, to obtain a high percentage of reactions with increased heat production in cats.

The influence of muscular movement in the production of increased thermogenesis may be disregarded as a source of error in interpretation of the results in these experiments. Movement in animals cannot be eliminated or satisfactorily controlled. The long observation period (two hours) and the great number of individual observations on each animal under relatively constant conditions eliminate the dangers of errors in interpretation which arise when the observation periods are short or when only a few scattered observation are made.

A criticism has been made that the higher respiratory quotients indicated the rabbits were not in the postabsorptive state. It should be pointed out that this is not possible in the rabbit. It requires four to six days of starvation to empty the stomach of a rabbit. Normally the rabbit's stomach is never empty and digestion is continuous, while the cat or dog stomach is usually empty within twelve hours after feeding. To attempt to work with rabbits in the postabsorptive state would introduce gravely abnormal conditions. Under ordinary conditions and twelve to fifteen hours after feeding, the respiratory quotients in rabbits range around 85 while in cats after similar time intervals the respiratory quotients range around 75.

Conclusions.

1. A prolonged absolute rise in heat production has been obtained in 82% of 33 rabbits in which both suprarenal glands were completely removed, and in 40% of 15 rabbits where the suprarenal function was crippled by freezing.

2. The period of increased heat production may last from a few days to several months — the longest period in which increased thermogenesis has been followed in an individual rabbit was 23 weeks.

3. The increased thermogenesis is in part dependent on the increased rate of discharge of the iodin containing hormone from the thyroid. The ability of the thyroid to store iodin or to produce this hormone is not impaired after suprarenal injury.

4. Infection, trauma, nerve injury, muscular movement and diet are not essential factors in the increased thermogenesis following suprarenal injury.

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NOTE: The respiratory exchange measurements were made by Miss Anna Cipra and Miss B. H. Lowe, to whom we wish to express our thanks.

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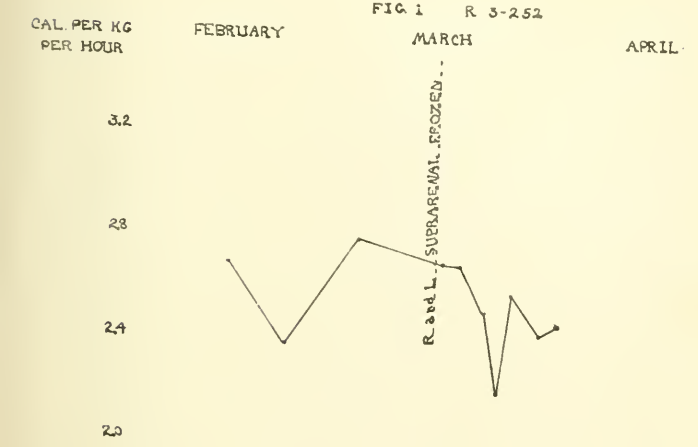
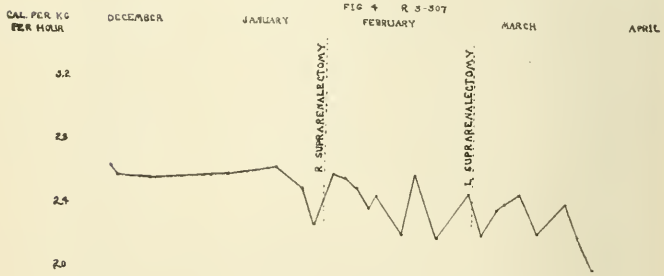




FIG 3 R 3-253



FIG 4 R 3-307



PANCREATIC DIABETES IN THE DOG.

VI. The Influence of Pancreatic Extracts Without the Aid of Alkali upon the Metabolism of the Depancreatized Animal.

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In a series of papers[1] published by the writers, 1913-1916, clear evidence of utilization of sugar in dogs made totally diabetic by removal of the pancreas, upon administration of pancreatic extracts was reported. Of the large number of experiments carried out from 1912 to 1916 inclusive several were omitted from these reports because of doubt at the time as to their import. The findings of Banting and Best[2] have offered an explanation of certain of these results. We feel therefore that they may be worth reporting even at this late day, because they lend support to the evidence furnished by Banting and Best, and because the technical difficulties make it improbable that just this support will soon be forthcoming otherwise.

As will appear in a later paper, the success of a method of preparation turns upon the reaction of the extracting medium. Most of the extracts prepared by us in 1912-1916 were made with acid media, but were neutralized or rendered alkaline with sodium carbonate or sodium hydroxide before administration. (Papers I and III.) In some of experiments reported here the method of preparation was different.

The first extract which we prepared from the pancreas of the ox in 1913 was made in saline solution. This extract was concentrated by evaporation at low temperature and was administered subcutaneously to dog "F" of our first series. This dog had been completely depancreatized on Jan. 21st, 1913 but, because he refused food, did not develop a complete Minkowski ratio of glucose to nitrogen in the urine. For this reason the effects of this injection were regarded as doubtful at the time. It is now certain however that the complete

TABLE I.

Dog F — Female. Depancreatized 1/21/13, 4 P.M.

Time	Total N grams	Total G grams	G:N	Temp.	DATE	REMARKS
4:30-2:30P.M.	4.73			37°C	1-21-1-22-13	Starvation.
-2:30P.M.	4.805	4.390	1.26	38.6°C	1-22-1-23-13	"
-2:30P.M.	3.465	6.10	1.48	38.7°C	1/23-24/13	At 3P.M. 3/23/13. Transfused 200G blood from normal dog.
	4.100	5.85	1.41	38.9°C	1/24-25/13	Starvation.
-2:30P.M.	4.144	1.100	1.54	39.2°C	1/25-26/13	Specimen only. Dog got out of cage and urinated.
2:30-2:30P.M.	0.750	1.345	0.52		1/26-27/13	Abdominal wound healing.
2:30-2:30P.M.	2.574	1.845	0.67		1/27-28/13	
-2:30P.M.	2.743	2.18	0.705		1/28-29/13	At 6P.M. injected 100 cc. of concentrated ext. of ox pancreas into left axilla. No abscess or induration followed.
-2:30P.M.	3.09	0.868	0.309		1/29-30/13	
	2.801	No sugar by Allihn or Benedict test			1/30/13	Wound healing rapidly.
	2.02	No sugar			1/31/13	
-2:53P.M.	1.934	2.37	0.488		2/1-2/3/13	Dog ate some meat.
-2:45P.M.	4.85	1.71	0.44		2/3-5/13	
					2/6/13	Fed 300G. beefheart.
-2:40P.M.	3.812	12.9	2.13	38.8°C	2/7/13	300G. beefheart. Slight suppuration in both wounds.
-12:30P.M.	6.03	13.5	2.29	38.6°C	2/7-8/13	
-12:50P.M.	5.877	2.70	0.74		2/8-9/13	Starvation.
-12:50P.M.	3.61	5.40	1.81	38°C	2/9-10/13	300G. beefheart.
	2.989	10.0	2.30		2/10-11/13	

disappearance of sugar from the urine, followed as it was by the development of a nearly complete diabetic ratio when the dog was later induced to eat meat, was due to the extract. The results are given in table I.

On January 23 the dog received 200 gm. of blood from a normal dog, but there was no significant effect[3] on the excretion of sugar in the twenty-four hour urine. Five days later 100cc. of the extract of ox pancreas in saline solution were injected into the left axilla immediately after catheterization and termination of the twenty-four hour period at 2:30 P.M. The excretion of sugar dropped from 2.18 gm. to 0.868 gm. *and the next two days was absent entirely.* It reappeared the following day when the dog began to eat. The dog ate 300 gm. of beefheart daily for two days bringing the G:N ratio up to 2.29. A starvation day brought it down to 0.74, when the same amount of food restored it once more to 2.30. This emphasizes the importance of gastric activity in the onset of diabetes after pancreatectomy in the dog as reported by Murlin and Sweet[4]. However neither starvation alone nor gastric repose suffices to clear the urine of sugar. *We are now convinced that the saline extract of ox pancreas was the cause.*

The importance of the reaction, not only in extracting the active principle in quantity but also in preserving it, is illustrated further by an experiment already reported[5] to which brief reference may be made. In our first paper the greatest success attending our efforts occured with dog IV which received 150cc. of a mixed extract of pancreas and duodenal mucous membrane by vein. The dog had been totally diabetic (Exp. V. p. 372). In two hours and twelve minutes sugar disappeared. Upon repetition of the experiment two days later (Exp. VI), when we were careful to make the extract distinctly alkaline, we were misled by the belief that the alkali (Na_2CO_3) had been wholly responsible for the effect. This was apparently confirmed by a third experiment (Exp. VII), in which the same quantity of 1% sodium carbonate in Ringer's solution alone produced a decline in the sugar excretion to the same hourly level and the same G:N ratio. This singular coincidence diverted our attention for several years to the alkali, although we were convinced in 1916 that the pancreatic extract played a part

in the various signs of improvement reported (See Paper III, p. 518). Recently upon going over our notes made at the time we found that the first extract (Exp. V) had been neutralized (to litmus) only but *had not been made* alkaline. The notation reads: "Immediately after washing the bladder at 6:00 P.M. started infusion by jugular* vein of a concentrated extract of the mucosae of two dog intestines (anesthetized with chloretone) and two pancreases. Continued infusion until 7 P.M. Extract prepared with acetic acid and N/5 HCl. Neutralized (after boiling) before final filtration."

The duodenal mucosae were included because of an idea that secretin or some constituent of the mucosa might be an activating agent for the internal as well as for the external secreting mechanism. This idea has not proved fruitful.

In discussing these last two experiments at the time (p. 375) we noted that "the dextrose elimination per hour and the G:N ratio reached the same level, at the end of four hours, as when the extracts of pancreas and doudenal mucosa were given. Certain points of difference however, may be noticed: (1) the effect is not immediate with the alkaline Ringer's solution alone; (2) the absolute fall in the sugar excretion is not so great; and (3) there is a marked diuretic effect with this solution while there was none with the organ extracts. These differences may prove to be significant, but, for the present it will be assumed that they are not so important as the likeness of results", etc. Misled by the remarkable effect of alkali alone we never returned to exactly this method of preparing the extract up to 1916.

Recently, the original experiment was repeated with complete success. *Not only was the sugar elimination stopped but the blood sugar showed a marked decline and the animal exhibited the power to burn glucose.*

Extraction of macerated pancreas by means of N/5 HCl and exact neutralization, *after boiling*, with sodium carbonate should therefore have demonstrated beyond a doubt the presence of the active principle essential to the combustion of sugar in 1913, and doubtless would have done so but for the similarity of effect (on the G:N ratio) of sodium carbonate alone. As matters stand, the credit for final and complete demonstration of the hormone (or enzyme) belongs to Bant-

* (The notation "femoral vein" in table p. 372 is an error.)

ing and Best[6]. It may be permissible however to remark[7] that the experiments reported by Murlin and Kramer in 1916 cannot be explained except upon the hypothesis that the active principle was present in the extracts employed by them. It is not to detract in the slightest degree from the brilliance of Banting and Best's achievement, but to confirm it that we are reporting in more detail than has hitherto been done the observations made nearly ten years ago.

Banting and Best seem to be of the opinion that heating the hormone to 57°C. kills it and therefore that it is of the nature of an enzyme. We have positive evidence, on the contrary, that under certain circumstances at least it will withstand boiling in acid medium. This point cannot be discussed further at present and is mentioned only to say that in our opinion the nature of the hormone is not yet demonstrated.

Another extract of cow's pancreas made up in Henderson's phosphate mixture proved to be potent for restoring to a limited extent the capacity to oxidize glucose.

Dog V., a 10 kg. female was depancreatized on June 6th, 1913. On the 19th a G:N ratio of 2.66 was found in the bladder urine at 11:45 A.M. In the afternoon respiratory quotients of 0.68 and 0.67 were obtained showing that the animal was completely diabetic.

On the 20th the dog was given a large dose of chloretone and when complete anesthesia was established was placed in the respiration apparatus and two periods obtained. Following this the animal was taken out, catheterized and given an infusion, by vein, of Ringer's solution. The venous cannula was left in place and the apparatus so arranged as to continue infusion after the animal had been returned to the respiration chamber. When the preliminary period had been completed and the observation period started the clamp was so adjusted as to permit a slow infusion throughout the respiration period.

The infusate was an extract of 4 ox pancreases which had been passed through a meat grinder directly into 1,000cc. of 1% Henderson's phosphate mixture[8]. Later HCl was added until the supernatant fluid was plainly acid to litmus, and extraction was allowed to continue for two hours at room temperature. It was then boiled quickly and filtered, after which it was made slightly alkaline with di-sodium phosphate in which condition it was administered to the animal.

[8] 1 gm. NaH_2PO_4 in 1000 cc.

TABLE II.

*Influence of pancreas extract in phosphate mixture.**

DATE 1913	Time P.M.	CO_2 liters	O_2 liters	R. Q.	Infusion Cc.
June 20—	3:22 - 4:22	2.948	4.426	0.666	
	4:22 - 5:22	3.002	4.306	0.697	
	INFUSION OF PANCREAS EXTRACT				
	9:02 - 10:02	3.841	5.143	0.747	?
	10:202 - 11:02	4.166	5.164	0.788	140
	11:02 - 12:02	4.039	5.601	0.721	120

The rise in respiratory quotient is not very great but is sufficient to indicate that the extract had some effect on combustion. Chloretone itself does not, in the experience of this laboratory, raise the respiratory quotient. Indeed, it often has the opposite effect[9]. *As was shown in an earlier paper at times the pancreas hormone does survive a degree of alkalinity amounting to N/20 NaOH.* Unfortunately, in the case before us, the degree of alkalinity or pH is not known.

One other experiment not previous reported deserves a place in the literature of the subject. Murlin and Sweet in following up observations made by us on the exclusion of the gastric contents from the intestine, as regards their effect on the onset and severity of the diabetes produced by pancreatectomy, reported several dogs which had been completely gastrectomized previous to pancreatectomy. One of these (dog XV) had shown some capacity to oxidize glucose eight days after extirpation of the pancreas (Table V, p. 282). On the tenth day, February 25th, 1916, the thyroids were removed, sparing the parathyroids. Three days later the urine showed a G:N ratio of 2.67 and respiratory quotients of 0.727 and 0.721. The next day, the fourteenth after pancreatectomy, at 12:30 P.M. the dog was given (subcutaneously and intravenously) 50cc. of a *suspension of finely ground pancreas* (from two dogs) which had been standing in Ringer's solution for three days under toluol. Twenty grams of glucose were also given in 10% solution intravenously.

The animal was placed in the respiration apparatus at 2 P.M. and three respiration period were obtained as follows:

* 9 gm. Na_2HPO_4.

TABLE III.

Influence of Suspension of Pancreas.

DATE 1916	TIME P.M.	CO_2 Liters	O_2 Liters	R. Q.
February 29th—	2:33 - 3:33	2.817	3.348	0.811
	3:33 - 4:33	2.755	3.458	0.797
	4:33 - 5:33	2.669	3.291	0.811

In spite of the 20 gm. of dextrose administered by stomach just before the respiration experiment the dog excreted up to 10:30 o'clock next morning only 7.83 gm. and gave at that time a G:N ratio of only 0.53. The animal was chloroformed on March 2nd. Careful search revealed no sign of pancreatic tissue.

That removal of the thyroids did not prejudice this result is conclusively proved by observations on two dogs from which the thyroids had been excised several weeks previously. These experiments also have not hitherto been reported.

Thyroid Dog I. Small, black longhaired female weighing 6.0 kgm. was deprived of the thyroid glands by Dr. Sweet on January 21st, 1916. The parathyroids with their blood vessels were scrupulously spared. A quick recovery followed. For three days thereafter the dog was fed on beefheart, crackermeal, lard and bone ash and then the crackermeal was dropped.

Respiration experiments were performed as follows:

TABLE IV.

Respiratory Metabolism of a Thyroidectomized Dog.

DATE 1916	Weight	TIME A.M.	CO_2 Liters	O_2 Liters	R. Q.	REMARKS
Jan. 27th—	6.25	10:07 - 11:07	1.804	2.245	.80	dog perfectly quiet
		11:07 - 12:07 P.M.	1.894	2.316	.81	" " "
Jan. 31st —	6.45	2:18 - 3:18	1.483	1.995	.74	" " "
		3:18 - 4:18	1.631	2.176	.75	" " "

The higher quotient on January 27th is referable to the carbohydrate component of the diet which at this time had not yet worn off. On a meat-fat diet the quotient was at the appropriate level. *There is no indication that removal of the thyroids alters in any way the handling of carbohydrates.*

Thyroid Dog II. White-faced bull, female, weighing 8.65 kgm. was thyroidectomized by Dr. Sweet on the same day as Dog I. The feeding also had been the same in quality though not in quantity up to time of the repiration experiments. On 400 gm. beefheart and 30 gm. lard daily the following results were obtained.

TABLE V.

Respiratory Metabolism of Thyroidectomized Dog.

DATE 1916	Weight kgm.	TIME P.M.	CO_2	O_2	R. Q.	Calories per hr.
Jan. 29th—	8.85	12:47 - 1:47	3.466	4.263	.80	19.91*
		1:47 - 2:47	3.467	4.544	.76	20.73
		A.M.				
Jan. 31st —	8.75	10:42 - 11:42	2.628	3.284	.80	15.41**
		11:42 - 12:42P.M.	2.685	3.494	.77	16.27

* After food.
** Basal.

Here also there is no sign that deprivation of the thyroids alone raised the respiratory quotient. We may be assured therefore that the higher quotients reported for Dog XV, when the pancreatic suspension was given, were really the outcome of a restoration in part of the capacity to oxidize glucose.

The experiment confirms the observations of Meltzer and Kleiner[10] and of Kleiner[11] alone that pancreatic suspensions added directly to the circulation tend to correct the diabetic state. Demonstration of a capacity to oxidize glucose, Kleiner appears to think, is wholly unnecessary, the reduction in blood sugar being quite sufficient proof of an active anti-diabetic agent. We might be inclined to agree with this opinion if it were yet established that the fundamental defect in diabetes is, as he believes, an alteration of permeability of the capillary wall whereby glucose is prevented from reaching the seat of oxidation. Without assuming to decide that this is not the case, or to say that Kleiner's evidence to this effect is not valuable, we submit that proof of a restoration of the power to burn sugar is *at once* proof of a restoration of the power to reach the seat of oxidation and that *it can be oxidized* when it arrives there. Kleiner misquotes the work of Murlin and Kramer stating (p. 154) that their unboiled extracts were given by mouth with Na_2CO_3, the inference apparently being that the rise in quotient which was reported was due to the liberation of CO_2 from the carbonate administered. *Not sodium carbonate but sodium hydrate was used in the experiments referred to.* In the light of the work of Banting and Best this degree of alkalinity (N/20) may have prevented the destruction of the active principle by the pepsin of the stomach; for of course it could not be destroyed by trypsin in a totally depancreatized dog, and it would escape destruction by this agent for a considerable time after

partial pancreatectomy. Further evidence of benefit from enteral administration of extracts will be supplied in a later communication.

Conclusions.

Additional proof is presented of the presence, in pancreatic tissue, of a substance capable of restoring to the diabetic animal the ability to utilize glucose.

Although these experiments were made during the years 1913 to 1916, they are presented to confirm the previously recorded observations of Banting and Best.

The nature of the active principle is yet to be determined.

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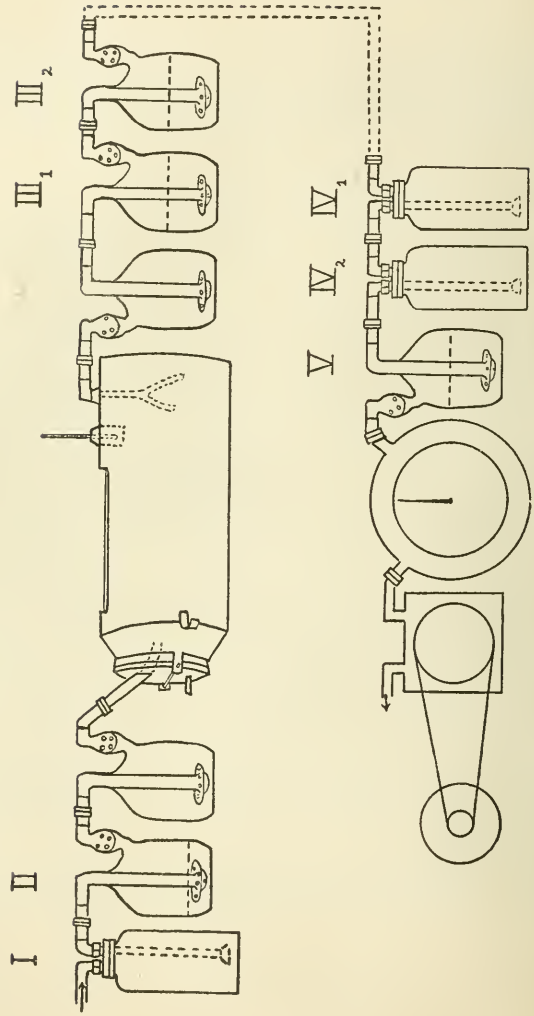
A MODIFIED HALDANE OPEN CIRCUIT APPARATUS FOR MEASURING THE RESPIRATORY EXCHANGE IN NEW BORN BABIES AND ALSO IN RABBITS AND CATS.

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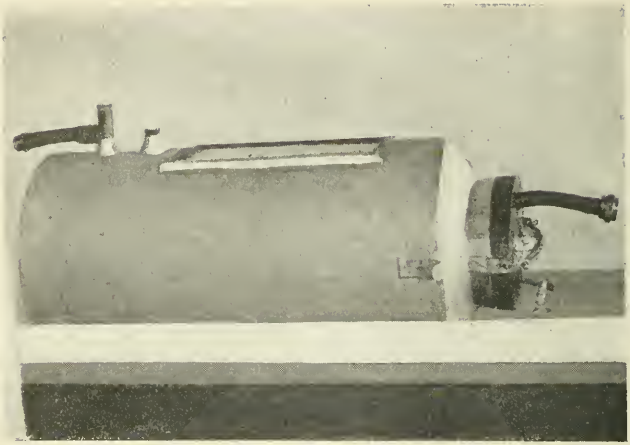
To our knowledge the Haldane[1] open circuit type of apparatus has not been used for measuring the respiratory exchange in infants. With proper precautions it is a very accurate means for determining the respiratory exchange in small animals including rabbits and cats. During the past three years we have made a great number of respiratory exchange measurements on cats and rabbits using a modified Haldane apparatus. Asher and his collaborators[2] have also modified the apparatus to accommodate rabbits. Many of the cats and rabbits studied were heavier than the average new born baby (3250 gm.) and as the normal heat production per kg. per hour is much greater both in the rabbit (2.40-2.50 cals.) and in the cat (2.15-2.25 cals.) than in new born infants (1.75-1.90 cals.)[3], it seemed to us that it could easily be adapted for the study of the respiratory exchange in infants. Because of its simplicity, ease of operation, relative cheapness and accuracy, the apparatus lends itself to the study of many of the problems involving heat production measurements in the new born. As only a very brief reference[4] has been made to the modifications required for its use with cats and rabbits it seems advisable to publish a more detailed description and criticism of the modifications for its use both with animals and with infants.

The apparatus as used for infants is shown diagramatically in Fig. 1. Outside air is drawn through a soda lime jar and


I
II
III1
III2
IV
IV2
IV1

through a Williams absorber containing a column of sulphuric acid sufficient to cover the perforations at the bottom of the intake tube to a depth of 2 cm., to take out the CO_2 and the water vapor. The air is next drawn through an empty Williams bottle into the chamber through a Y tube to split and scatter the air current. The air is withdrawn from the opposite end of the chamber through another Y tube, the open ends of which extend to within 5 cm. of the bottom of the chamber, into another empty Williams bottle and into one or two Williams bottles of approximately 1200 cc. capacity and containing 750 cc. of sulphuric acid (one Williams bottle contaning this amount of sulphuric acid, sp. g. 1.83-1.85, will take out all the water vapor from an air current of 30 liters per minute)[5]. The second bottle of sulphuric acid is therefore not necessary but has been used by us merely as an additional factor of safety and to get data regarding completeness of removal of the water by the first sulphuric acid bottle under varying rates of ventilation and degrees of saturation of the sulphuric acid with water. Next the air is drawn through one or two soda lime jars. One soda lime jar (1800 cc. capacity) is ample to absorb all the CO_2 from an air current of 35 liters per minute[6] if the soda lime is renewed when it has gained 75 gm. CO_2. The air then passes through another Williams bottle to take out the water constantly given off from the moist soda lime and then through a gas meter and a Crowell blower. All connections must be tight and as short as possible and are made with ½″ rubber tubing wired both to the bottles and the couplings. Standard commercial ⅜″ brass steam couplings used with rubber washers are very satisfactory; the cheaper garden-hose couplings are unsatisfactory. We have used glass wool plugs loosely packed in the outlets of all Williams bottles and believe it aids catching the unweighable sulphuric acid spray.

The chamber used for infants is shown in Fig. 2. It consists of a truncated box made of copper or zinc 56 cm. in length, 25.5 cm. in width and flattened slightly on the bottom. The cubic capacity is 23.5 liters. The infant is introduced feet first through an oval opening 19.5 x 15 cm. which readily admits a baby of 4500 gm. with the necessary wrappings and blankets. The opening or mouth of the chamber is closed with a cork stopper 3 cm. in thickness, the pores of which



have been filled with shellac, and sealing is accomplished by using rubber grease thickened by the addition of powdered talc. This makes an exceedingly light, cheap, simple and rapid



means of closing the chamber. The stopper is held in place by a spring steel rod and adjustable lugs. The stopper is pierced by the air intake tube and another small tube for attaching a manometer. An observation window 10 x 20 cm. is provided and just behind this window is an opening for the thermometer. The weight of the chamber, complete, is approximately 2620 gms. The whole apparatus is mounted on felt pads which reduce the vibration produced by the air passing through the sulphuric acid.

The chamber used for cats and rabbits is shown in Fig. 3. It is made of hard glass blown to the shape of a large wide mouth bottle and flattened slightly on one side.* The jar measures 41 cm. in length x 18 cm. in diameter and has a cubic capacity of approximately 9.2 liters. This amount of air space is ample to meet the needs of a cat or rabbit during weighing, as the time required rarely exceeds two minutes. The mouth of the chamber is circular in shape (an oval opening would be better if it could be made) and 11.5 cm. in diameter and is closed with a cork stopper in the manner mentioned above.

As the O_2 is determined indirectly by weight, accurate balances protected from air currents are necessary. We have used Sauter balances of 10 kg. capacity as recommended by Benedict. Balances of this make may be adjusted to weigh a 10 kg. load to plus or minus 25 mg. The CO_2 is determined directly by the gain in the soda limes and the last Williams bottle which are weighed together. The O_2 is determined by subtracting the loss in weight of the chamber from the sum of the gains in bottles 4, 5, 6, 7, 8 and 9. (See Fig. 1). Bottles 4, 5 and 6 may be weighed together. Bottles 6 and 8 serve only as factors and when operating with skilled assistants are preferably omitted. Bottles 3 and 4 in addition to serving as traps also act as sound mufflers. They are undoubtedly important aids to the comfort and quietness of the animal.

The comparative accuracy of the Haldane method may be tested in several ways. Fridericia[7] modified the apparatus so that it could be used either as a closed or open circuit. He found that the indirect method of O_2 determination checked with the direct method. A simpler check or test is to run blank experiments. This procedure tests both for tightness of the

* We wish to acknowledge our indebtedness to the Libby Glass Co., Toledo, Ohio, for making these jars.

connections and the accuracy in weighing. If the apparatus is suitable for use it should give zero, or at most, values of only a few milligrams for both O_2 and CO_2. The graphic method of recording movement and respiration as introduced by Benedict and Homans[8] could be attached though we have not done so. In the work with babies the more laborious method of constant observation was used because we desired to study also the appearance and behavior of the child under these conditions. The apparatus in operation, and connected as above described, shows a negative pressure in the chamber of from 40 to 45 mm. of water. This negative pressure is due mainly to the column of sulphuric acid in bottle 2, and the above pressures obtain only when the column of sulphuric acid is not greater than 2 cm. and the rate of ventilation not over 4 liters per minute. The rate of ventilation may be varied at will by means of a cutout placed just in front of the blower. With cats and rabbits we have found that 3 liters of air per minute prevents the deposition of moisture in the chamber with room temperatures around 20°. Asher used two liters of air per minute for rabbits. New born babies are comfortable with a ventilation of 3 to 5 liters per minute. With this rate of ventilation the chamber temperature taken every five minutes has varied within a degree during the hour in a series of 97 experiments. We have not used the apparatus with normal babies over thirty-five days old.

For cats and rabbits a two hour observation period has been adopted as standard and for babies a one hour period. With babies under two weeks old no difficulty is encountered in getting them to sleep the full hour if prepared and fed just before starting. Older babies are more restless and it is more difficult in spite of these precautions to obtain a full hour's observation without waking.

The following protocols are given to illustrate the method of recording the data obtained:

PROTOCOL NO. 1.

Date: Nov. 25, 1921.
Exp. No. 393.
Cat No. 13 (adult-female)
Weight of Cat: 2740 gms.
Began Exp. 1.43 P.M.: Duration 2 hours.
Temp. of room 21.0°C.
R. Q. 76
Total Calories per 2 hrs. = 13.43.
Cal. per Kg. per hr. = 2.45
III = 2244.77 — 2246.45
IV = 3813.30 — 3817.38
V = 2256.29 — 2256.43
Chamber and Cat 6198.82 — 6196.98

III = 2245.45
2244.77
1.68
IV = 3817.38
3813.30
4.08
V = 2256.43
2256.29
.14
Chamber and Cat = 6198.82
6196.98
1.84

$4 + 5 = CO_2 = 4.22$ gms.
$4 + 5 + 3$ — Chamber Loss $= O_2 = 4.06$ gms.
$\frac{4.22}{4.06} \times \frac{32}{44} =$ R. Q. $= 75.5$

Behavior of animal — awake, quiet.

NOTE: R. suprarenal removed.
L. " frozen.

PROTOCOL NO. 2.

Date: June 1, 1922.
Exp. No. 78.
Baby No. 1-S (female, 33 days of age).
Weight of Baby: 3995 gm.
Began Exp. 11.35 A.M.: Duration 1 hour.
Temp. of room 25.0°C.
R. Q. 97.0
Total Calories per hour = 9.23.
Cal. per Kg. per hour = 2.31
III = 3872.05 — 3875.53
IV = 6890.88 — 6893.97
V = 1685.62 — 1686.04

III = 3875.53
3872.05
3.48
IV = 6893.97
6890.88
3.09
V = 1686.04
1685.62
.42
Chamber and Baby = 7219.43
7215.07
4.36

$4 + 5 = CO_2 = 3.51$.
$4 + 5 + 3$ — Chamber Loss $= O_2 = 2.63$ gms.
$\frac{3.51}{2.63} \times \frac{32}{44} =$ R. Q. $= 97.0$

Chamber and Baby = 7219.43 — 7215.07.

Time min.	TEMPERATURES room	chamber	Respiration	Condition of Baby
0	24.5	28.0	60	Sleeping soundly
5		28.2	58	" "
10		27.7	60	" "
15		27.5	46	" "
20		27.4	46	" "
25		27.4	52	" "
30	23.5	27.6	54	" Coughed once
35		28.0	50	" Moved hand
40		28.3	46	" soundly
45	23.8	28.0	44	" Coughed once
50		27.8	46	" Soundly
55		27.6	46	" "
60		27.5	48	" "

TABLE IX.

Effect of using a tourniquet.

NAME	Method of taking blood	0_2 Content	0_2 Cap.	% Sat.
Charles Brown Post-operative adhesions Not fasting	No. 1. — No tourniquet.	6.19	20.79	29.79
	No. 2.—Tourniquet on about 2 min. Arm blue.	8.85	19.02	46.55
William Evans Ulcer of rectum Not fasting	No. 1. — No tourniquet.	13.64	19.38	70.38
	No. 2.— Usual technique.	19.45	21.58	90.12
	No. 1. — No tourniquet.	19.25	21.95	87.69
	No. 2.— Usual technique but 15 min. later.	17.97	21.95	81.86
Charley Baldwin Typhoid Convalescent Fasting	No. 1. — No tourniquet.	15.7	20.74	75.69
	No. 2.— Usual technique.	17.64	21.17	83.31
Joseph Franchino Mitral insufficiency Fasting	No. 1. — No tourniquet.	15.28	23.53	64.93
	No. 2.— Usual technique.	15.72	20.99	74.87
William Archibald Mitral insufficiency Not fasting	No. 1. — No tourniquet.	11.51	21.47	53.6 %
	No. 2.—Usual technique.	11.08	20.36	54.42 %

NOTE: Except where stated otherwise, the needle was not withdrawn from the vein between samples No. 1 and No. 2.

"Usual technique" means that the tourniquet was left on about ½ minute before sample was collected.

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FURTHER EXPERIMENTS WITH HIGH FAT DIETS IN DIABETES.

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As stated in a former paper[1], the experiences in this Institute support the view that limitation of total calories is one of the essentials of the diabetic diet. High fat diets have been tried repeatedly with uniformly injurious results, which become manifest quickly in severe cases and more slowly in milder cases.

Our views therefore disagree with those of Newburgh and Marsh[2] and agree more closely with those of Joslin[3]. The suggestion of Woodyatt[4] has been adopted in reckoning the glucose value of fat though our results demonstrate the additional influence of caloric variations. The following three illustrative cases are chosen for publication because urinary nitrogen analyses were performed, while the diets were kept free from soup or other disturbing factors. Blood samples were taken mornings before breakfast, and the plasma was analysed for sugar by Benedict's method.

Patient No. 1065 was a girl aged 15 years, with negative family history. Her own history was that of a normal child, without infections or other known factors in direct relation to the onset of the diabetes. In 1920 symptoms of thirst, polyuria and loss of weight led to the finding of glycosuria. On restricted diet, glycosuria has since been kept absent most of the time, but the blood sugar has not been controlled, and loss of tolerance has been marked. The patient was admitted January 4, 1922 and discharged June 4, 1922.

The physical examination was negative except for emaciation. Because of the heavy ketonuria, the diet up to January 8 was 20 gm. protein and 20 gm. carbohydrate daily. From January 9 to March 11, it varied from 10 to 20 gm. of protein per day without other food, and with 17 days of complete fasting interspersed. The plasma sugar was 0.600% at the first examination, and fell very slowly under the extremely rigorous regime, reaching a normal level for the first time on March 10. With a height of 5 feet 5 inches, the patient's weight at admission was 80 pounds. This rose by invisible fluid retention to 92 pounds on February 1, then fell gradually to 75 pounds by March 10. The further record is contained in Table I.

TABLE I.

Date 1922	Weight lb.	DIET				BLOOD		URINE			
		Protein gm.	Fat gm.	CH. gm.	Total Calories	Plasma sugar mg. per 100cc.	Blood urea mg. per 100cc.	Volume cc.	Qualitative Dextrose	Nitro Prusside reaction	Total Nitrogen gm.
March 1	77	—	—	—	—	—	—	—	0	0	—
" 2		10	4	—	—	—	—	—	0	0	—
" 3	78	10	4.7	—	—	.143	—	—	0	0	—
" 4		10	4	—	—	—	—	—	0	0	—
" 5	78	10	8	—	—	—	—	—	0	0	—
" 6		10	5	—	—	—	—	—	0	0	—
" 7	74	10	7	—	—	.133	—	—	0	0	—
" 8		15	6	—	—	—	—	—	0	0	—
" 9	75	15	5	—	—	—	—	—	0	0	—
" 10		15	8	—	—	.109	—	—	0	0	—
" 11	75	15	5	3	—	—	—	—	0	0	—
" 12		15	19	3	—	—	—	—	0	0	—
" 13	73	20	23	3	299	—	—	4650	0	0	7.4
" 14		20	23	3	299	.138	—	4380	0	0	3.8
" 15	72	11	11	1	147	.111	—	5180	0	0	5.4
" 16		20	34	3	398	—	—	3440	0	0	6.4
" 17	71	25	34	3	418	.122	—	3220	0	0	6.1
" 18		23	34	3	418	—	—	2630	0	0	6.7
" 19		25	16	5	264	—	—	3080	0	ft.	5.7
" 20		25	15	5	255	—	—	3330	0	0	7.0
" 21	73	25	9	5	201	.95	—	4030	0	0	7.8
" 22		25	12	5	228	—	—	3980	0	0	6.9
" 23	73	25	12	5	228	—	—	3850	0	0	6.2
" 24		25	12	5	228	—	—	3980	0	0	6.5
" 25	72	25	50	5	570	.113	—	3480	0	0	6.3
" 26		25	50	5	570	—	—	3440	0	0	5.8
" 27	73	25	50	5	570	—	—	3080	0	0	5.0
" 28		25	50	5	570	.132	—	3085	0	0	5.6
" 29		25	50	5	570	—	—	2780	0	0	4.6
" 30		25	50	5	570	.168	—	2290	0	0	3.8
" 31	73	25	50	5	570	—	—	2460	0	0	5.4
April 1		25	50	5	570	—	—	2150	0	0	4.5
" 2	73	25	50	5	570	.206	—	2090	0	0	3.5
" 3		25	12	5	228	—	—	1540	0	0	4.2
" 4		25	12	5	228	—	—	2100	0	0	4.8
" 5		25	10.7	5	226	—	—	2240	0	0	10.5*
" 6		25	12.8	5	245	.099	—	2870	0	0	7.8
" 7		25	12.1	5	239	—	—	3090	0	0	8.2
" 8	74	27	13	5	245	—	—	2690	0	0	7.3
" 9		30	13	5	257	—	—	2970	0	0	8.5
" 10	71	50	27	5	463	—	—	2690	0	0	8.5
" 11		50	24	5	436	—	—	2970	0	0	9.4
" 12	70	50	31	5	499	—	—	2630	0	0	9.7
" 13		50	23	5	535	—	—	2660	0	0	9.2
" 14	71	50	23	5	427	—	—	2470	0	0	5.7
" 15		50	21	5	409	—	—	2610	0	0	8.4
" 16		50	12	5	328	—	—	1430	0	0	6.6
" 17		50	9	5	301	—	—	2700	0	0	9.3
" 18	70	50	9	5	301	—	—	2880			10.1

Note: ft. = faint
* Rise of nitrogen due to long starvation?

TABLE I. (*Continued*).

Date 1922	Weight lb.	DIET				BLOOD		URINE			
		Protein gm.	Fat gm.	CH. gm.	Total Calories	Plasma sugar mg. per 100cc.	Blood urea mg. per 100cc.	Volume cc.	Qualitative Dextrose	Nitro Prussside reaction	Total Nitrogen gm.
April 19		40	100	5	1080	—	—	2610	0	0	8.7
" 20	70	40	100	5	1080	—	—	2430	0	0	6.4
" 21		40	100	5	1080	—	—	2100	0	0	5.9
" 22	72	40	100	5	1080	—	—	2100	0	0	4.5
" 23		40	100	5	1080	—	—	1350	0	0	3.7
" 24	71	40	100	5	1080	—	—	1920	0	0	3.2
" 25		40	100	5	1080	.230	—	2060	0	0	5.7
" 26	74	40	100	5	1080	—	—	2030	ft.+	ft.	5.6
" 27		40	100	5	1080	.319	—	3290	ft.+	ft.	10.2
" 28	76	40	14	5	306	—	—	3050	ft.+	ft.	6.1
" 29		40	17	5	333	.326	—	2080	0	0	7.4
" 30	78	40	—	5	180	—	—	2320	0	0	6.1
May 1		40	14	5	306	—	—	2430	0	0	6.8
" 2	79	40	19	5	351	—	—	2380	0	0	6.9
" 3		40	17	5	333	.132	—	2560	0	0	7.1
" 4	80	40	19	5	351	—	—	3640	0	0	8.1
" 5		45	20	5	380	—	—	3360	0	0	6.2
" 6	78	45	18	5	362	.110	—	2900	0	0	9.3
" 7		45	55	5	695	—	—	2030	0	0	5.2
" 8	77	45	55	5	695	—	—	3310	0	0	7.4
" 9		45	55	5	695	—	—	2350	0	0	7.3
" 10	74	45	55	5	695	.136	—	2200	0	0	7.1
" 11		40	57	5	693	—	—	3160	0	0	6.4
" 12	75	40	57	5	693	—	—	2300	0	0	6.7
" 13		40	57	5	693	.120	—	2660	0	0	7.4
" 14	75	40	57	5	693	—	—	3070	0	0	8.3
" 15		40	68	5	792	—	—	2630	0	0	6.6
" 16	74	40	68	5	792	.136	—	2160	0	0	5.5
" 17		40	68	5	792	—	—	3530	0	0	9.5
" 18	74	40	68	5	792	—	—	2470	0	0	6.2
" 19		40	68	5	792	.187	—	2450	0	0	6.7
" 20	74	40	68	5	792	—	—	3230	0	0	6.5
" 21		20	fast	2	88	—	—	3490	0	0	6.2
" 22	75	40	68	5	792	—	—	2550	0	0	8.3
" 23		40	68	5	792	—	—	2670	0	0	7.1
" 24	74	40	68	5	792	.166	—	2210	0	0	5.1
" 25		35	48	5	592	—	—	2630	0	0	5.2
" 26	74	35	48	5	592	—	—	2950	0	ft.	7.3
" 27		35	48	5	592	.166	—	3650	0	ft.	5.5
" 28	74	20	—	2	88	—	—	3300	0	0	5.4
" 29		35	48	5	592	—	—	2540	0	0	4.3
" 30	74	35	48	5	592	.162	—	3430	0	0	4.8
" 31		35	48	5	592	.112	—	3650	0	0	6.5
June 1	75	40	57	5	693	—	—	2700	0	0	4.5
" 2		40	57	5	693	—	—	2690	0	0	5.2
" 3	75	40	57	5	693	.150	—		0	0	—

Note: ft. = faint

The desperate character of the case is indicated by the length of time and the extreme privations required to control the hyperglycemia. It is remarkable that a fifteen year old girl, already emaciated, could survive a period of more than two months on a diet which averaged less than 15 gm. protein and 5 gm. fat per day. The clinical result was that which is usual in such cases. At first the undernutrition markedly improved the strength, by clearing up the sugar and acetone. With further undernutrition the strength gradually declined, and, as usual, a normal blood sugar was accompanied by a feeling of marked weakness. On the other hand, there was no dangerous prostration, and the patient was at no time confined entirely to bed. The small protein allowance was probably the means of maintaining the strength to this extent. The use of non-nutritious "fillers" in the diet as usual obviated any extreme suffering from hunger.

Beginning with 15 gm. protein, 3 gm. carbohydrate and 5 gm. fat on March 11, the diet was gradually increased as shown in the table. Up to March 24, the diet of 25 gm. protein, 5 gm. carbohydrate and 12 gm. fat was tolerated in such manner that a normal plasma sugar of 0.113 per cent. was still present before breakfast on March 25. March 25 to April 2, the fat ration was increased to 50 gm. daily, leaving the protein and carbohydrate the same as before, and thus raising the total calories to 570 daily. The influence upon the plasma sugar was manifest as early as March 28, with the slight rise to 0.132 per cent., and the hyperglycemia steadily increased to 0.206 per cent. on April 2. Reduction of the fat to 12 gm. daily, without other change in the diet, resulted in a rapid fall of the plasma sugar to 0.099 per cent. on April 6 and to 0.076 per cent. on April 9.

In this experiment, no subtraction from the other foods was made to allow for the theoretical glucose value of the fat, because it was considered that the small quantity of fat added would merely replace body fat in metabolism without appreciably altering the total combustion. The slight fall in the urinary nitrogen suggests a slight action of the fat in sparing protein. The chief value of the nitrogen analyses is as a reminder of the well known fact that even in extreme emaciation the chief source of calories is always fat, and the protein breakdown remains comparatively low until a premortal

stage is reached. Furthermore, the tendency with advancing emaciation is toward very low, not toward high blood sugar values. In the present instance, the continued undernutrition raised the tolerance in such manner that normal blood sugar values were maintained from April 10 to 19 with increases of diet to 50 gm. protein and 9 to 31 gm. fat. During this period the urinary nitrogen was higher than before, frequently between 8 and 10 gm. per day. The hyperglycemia from fat feeding appears thus to be not explainable by changes in the quantities of protein or glucose metabolized.

April 19 to 27, the fat ration was raised to 100 gm. daily, while the protein was reduced to 40 gm. and the carbohydrate kept constant at 5 gm. The total calories were thus increased to 1080. The plasma sugar showed the usual gradual rise, and by April 27 had reached 0.319 per cent. Glycosuria and ketonuria appeared. The formerly clear plasma became markedly turbid during digestion and still retained some cloudiness in the fasting samples before breakfast. Sharp reduction of the fat intake, beginning April 28, failed to halt the symptoms immediately. The familiar delayed action of fat was perceptible in the further rise of plasma sugar to 0.326 per cent. on April 29. With no further change in the diet, however, glycosuria and ketonuria ceased, and the plasma sugar by May 6 had returned to normal. The urinary nitrogen analyses apparently indicate a slight sparing of protein by the fat. In particular, they serve to exclude any increased protein catabolism as an explanation of the hyperglycemia and glycosuria from fat feeding.

The remainder of the table represents the attempt to build up a diet sufficient to support life while keeping the blood sugar normal. Study of the figures will show that 700 calories represented about the limit of tolerance. The increase to 792 calories, beginning May 15, resulted in definite hyperglycemia, which was reduced by the subsequent reduction of diet to 35 gm. protein, 5 gm. carbohydrate and 592 calories. The patient left to continue treatment at home before the purpose of the institutional regime had been fully accomplished.

The diet at home has ranged between 600 and 800 calories. Though it has apparently been managed accurately, the results as usual have been slightly worse than in an institution. Glycosuria and ketonuria have been kept absent, but slight hyper-

glycemia has been the rule. The bodily weight and strength remain about the same. The weakness is such that the child prefers to spend the greater part of each 24 hours in bed, but nevertheless is up and dressed several hours every day and is able to enjoy automobile rides and other light amusements. The ultimate prognosis under such treatment is fatal, partly because the low diet must entail a slow loss of body tissue which is temporarily masked by water retention, and partly because a gradual decline of tolerance must occur in a case of this type with hyperglycemia. Thorough treatment would have required lowering of the weight by several more pounds, thus establishing a tolerance for a higher diet. These incomplete results would not have been permitted, except for hopes of future aid from pancreatic extract. For the present the child is safe and reasonably comfortable, and especially is free from the symptoms and rapid downard progress which must result from attempts to increase the diet with any kind of food. The loss of 195.4 gm. of total nitrogen in 82 days (reckoned on the urine alone, without consideration of the small additional quantities lost through the feces) is notable as an example of what can be borne by an already emaciated child. It is an unfortunate fact that diabetes of this extreme severity has never been controlled by any means other than extreme undernutrition.

Patient No. 1083 was a widow aged 67 years, with negative family and personal history. About 12 years ago she had a severe tonsillitis and was very ill for three or four days. A few days later she noticed unquenchable thirst with polyuria. Her weight, which had been 150 pounds, diminished within six weeks by 26 pounds. She consulted no physician, and the weight remained at the same low level until 2 years ago, when it increased to 135 pounds. One year ago thirst and polyuria again became noticeable. A physician consulted then found glycosuria of 2.5%. Moderate restriction of carbohydrate cleared up the glycosuria, which returned, however, within a few months. Four months ago polyphagia became prominent for the first time. Acetonuria had been slight, but much sodium bicarbonate had been taken. She was admitted to the Physiatric Institute March 10, 1922 and discharged May 19, 1922.

The physical examination was negative except for emaciation and weakness. With a height of 5 feet 1 inch, the weight was 97 pounds. March 10 to 14, the diet was 30 gm. protein and 10 gm. carbohydrate, and from March 15 to 24 it was 30 gm. of protein alone. On March 24 the urine became sugar free for the first time. The weight had gradually risen to 104 pounds by invisible water retention. The plasma

TABLE II.

Date 1922		Weight lb.	DIET				BLOOD		URINE			
			Protein gm.	Fat gm.	CH. gm.	Total Calories	Plasma sugar mg. per 100cc.	Blood urea mg. per 100cc.	Volume cc.	Qualitative Dextrose	Nitro Prussido reaction	Total Nitrogen gm.
March	25		10	5	—	85	—	—	2325	0	0	3.8
"	26	102	fast		—	—	.246	—	2535	0	0	4.6
"	27		fast		—	—	—	—	2290	0	0	4.6
"	28	101	30	6	—	174	.199	—	lost	0	ft.	3.7
"	29		30	—	—	120	—	—	1880	0	ft.	4.3
"	30	101	30	8	—	192	—	—	2600	0	ft.	2.0
"	31		30	8	—	192	.182	—	2630	0	ft.	6.6
April	1	100	30	13	—	237	—	—	2120	0	ft.	6.5
"	2		30	8	—	192	.242	—	3420	0	ft.	7.2
"	3	100	30	6	—	174	—	—	2000	0	ft.	4.5
"	4		30	20	—	300	—	—	1890	—	—	4.9
"	5	100	30	100	—	1020	—	—	2510	—	—	5.9
"	6		30	100	—	1020	.220	—	2330	—	—	5.2
"	7	98	30	100	—	1020	—	—	2560	—	—	6.9
"	8		30	100	—	1020	—	—	3090	0	ft.	6.5
"	9	96	30	100	—	1020	.171	—	1550	0	ft.	3.1
"	10		30	100	—	1020	—	—	1660	0	ft.	3.7
"	11	97	30	100	—	1020	—	—	1840	0	ft.	6.5
"	12		30	102	—	1038	—	—	2220	0	ft.	6.2
"	13	96	30	100	—	1020	—	—	1950	—	—	5.7
"	14		30	100	—	1020	.187	—	2000	0	0	6.8
"	15	96	30	100	—	1020	—	—	2420	0	0	4.8
"	16		30	150	—	1479	—	—	1810	0	0	3.1
"	17	96	30	150	—	1479	—	—	1920	0	ft.	—
"	18		30	170	—	1650	—	—	—	0	ft.	—
"	19	97	30	181	—	1749	.168	—	—	0	ft.	5.9
"	20		30	162	—	1678	—	—	1860	0	ft.	5.5
"	21		30	200	—	1920	—	—	1600	0	ft.	4.0
"	22		30	200	—	1920	.166	—	2370	0	ft.	6.0
"	23	95	30	196	—	1884	—	—	1750	0	ft.	5.6
"	24		30	200	—	1920	—	—	2110	0	0	7.5
"	25	95	30	200	—	1920	.265	—	—	0	ft.	—
"	26		30	200	—	1920	—	—	—	0	0	—
"	27		30	177	—	1713	.275	—	—	0	ft.	—
"	28	95	30	11	5	239	—	—	—	0	ft.	—
"	29		30	14	5	266	.238	—	—	0	ft.	—
"	30		30		5	104	—	—	1840	0	ft.	3.6
May	1		30	11	5	239	—	—	2010	0	ft.	6.8
"	2	95	30	11	5	239	—	—	2010	0	ft.	6.4
"	3		30	10	5	230	.162	—	1960	—	—	6.0
"	4	95	30	10	5	230	—	—	1620	0	0	5.4
"	5		40	10	5	270	—	—	2180	0	0	5.4
"	6	94	40	12	5	288	.203	—	2000	0	ft.	5.9
"	7		40	46	5	594	—	—	1900	0	ft.	5.8
"	8	94	40	46	5	594	—	—	1650	0	ft.	6.7
"	9		40	46	5	594	.152	—	2180	0	ft.	8.1
"	10		50	64	5	806	—	—	—	—	—	—
"	11	93	50	64	5	806	—	—	—	—	—	—

Note: ft. = faint

TABLE II. (*Continued*)

Date 1922		Weight lb.	DIET				BLOOD		URINE			
			Protein gm.	Fat gm.	CH. gm.	Total Calories	Plasma sugar mg. per 100cc.	Blood urea mg. per 100cc.	Volume cc.	Qualitative Dextrose	Nitro Prusside reaction	Total Nitrogen gm.
May	12	94	50	64	5	806	.125	—	1040	0	ft.	8.1
"	13		50	64	5	806	—	—	1820	0	ft.	10.19
"	14	92	50	95	10	1263	—	—	2300	neg.	ft.	10.43
"	15		50	95	10	1263	—	—	1900	0	ft.	10.43
"	16	94	50	95	10	1263	—	—	1960	0	ft.	9.0
"	17		50	95	10	1263	.143	—	1770	—	—	9.5
"	18	93	55	115	10	1295	.133		1950	0	ft.	10.6

Note: ft. = faint

sugar at the first examination was 0.783%, and gradually fell in parallel with the urinary sugar. The further record is contained in Table II.

The fast-days of March 26 and 27 reduced the plasma sugar from 0.246 to 0.199 per cent. On the ensuing diet of 30 gm protein with trivial quantities of fat, the plasma sugar fluctuated between 0.182 and 0.242 per cent.

Beginning April 5, the fat ration was raised to 100 gm. daily. The result was an actual fall in the plasma sugar, to 0.171 and 0.187 per cent. This result may have been attributable to the feeding, possibly by reason of a slight reduction of protein catabolism as indicated by the urinary nitrogen. On the other hand, the changes may have been purely accidental, like the preceding ones. Furthermore, this increase of fat had raised the total diet only to 1000 calories, and a continued improvement of tolerance might be expected from such undernutrition in such a case. Beginning April 16, the fat allowance was further increased, first to 150 and then to 200 gm. per day. There was the usual delay in effect. The plasma sugar by April 22 had fallen to 0.166 per cent; but by April 25 it had risen to 0.265 and by April 27 to 0.275 per cent. The patient also felt weaker and more depressed than on the previous very low diets.

Beginning April 28, the fat intake was reduced to a minimum, while the protein was kept constant and 5 gm. of carbo-

hydrate was added. The plasma sugar fell gradually to 0.162 per cent. on May 3. An increase of protein to 40 gm. on May 5 caused a rise of sugar to 0.203 per cent. on May 6. The marked undernutrition, however, resulted in a rapid increase of tolerance, so that with increase of protein to 50 gm. and of total calories to 800 the plasma sugar by May 12 was down to 0.125 per cent. By May 18 the patient was assimilating a diet of 55 gm. protein, 10 gm. carbohydrate and 1300 calories, with plasma sugar of only 0.133 per cent. during digestion. This gain was accomplished with a seeming reduction of only 4 pounds below the initial body weight. In reality, a greater loss of tissue was masked by water retention. The urinary nitrogen figures, balanced against the ingested protein, indicate a loss of 23.9 gm. of body nitrogen for the period March 25 to May 18, without counting fecal nitrogen and without mention of the period of severe privation between March 10 and 25.

The clinical picture showed the usual variations; first a gain of strength and well-being as the active diabetis symptoms were relieved, then a decline of strength with further undernutrition, a temporary malaise with the high fat experiment and relief after reduction of fat, and a decided improvement in all respects with the final diet of 1300 calories. Continuance of treatment at home has readily raised the tolerance to 60 gm. protein, 20 gm. carbohydrate and 1600 calories. In view of the age, and the attendant good prognosis and little tendency to downward progress, rigidly normal blood sugars have not been required, but is has been required that the analyses at all times of the day shall remain below 0.2%. The case illustrates diabetes in later life, which has been neglected through its mild stages until it has reached a final stage of severity and emaciation. Arrest and improvement of the condition is obtained only by limitation of the total diet and body weight, frequently involving an initial period of stringent privation. The improvement is then more easily maintained and the prognosis is better than in youthful cases of apparently equal severity.

Patient No. 177 was a Jewess aged 25, with negative family history. Her life had been free from known infections except measles in childhood, and obesity, gluttony and other predisposing causes of diabetes were also lacking. Diabetes began with increased hunger, thirst and urine in April, 1919. The diagnosis was made immediately, and diet restrictions were imposed, first at home, and later in a hospital, with the result of only two weeks' freedom from glycosuria. She was first

TABLE III.

Date 1922	Weight lb.	DIET					BLOOD		URINE					
		Protein gm.	Fat gm.	CH. gm.	Na Cl gm.	Total Calories	Plasma sugar mg. per 100cc.	Blood urea mg. per 100cc.	Volume cc.	Qualitative Dextrose	Nitro Prusside reaction	Total Nitrogen gm.	Acetone 24 hrs. gm.	
March 8		10	4	—	—	76	—	—	—	—	—	—	—	
" 9	82	10	4	—	—	76	—	—	—	0	0	—	—	
" 10		10	4	—	—	—	—	—	—	0	0	—	—	
" 11	74	10	3	—	—	—	—	—	—	0	0	—	—	
" 12		10	2	—	—	—	.145	—	—	0	0	—	—	
" 13	80	20	15	—	—	—	—	—	—	0	0	—	—	
" 14		20	16	—	—	—	—	—	—	0	0	—	—	
" 15	82	20	11	—	—	—	—	—	—	0	0	—	—	
" 16		20	14	—	—	—	.150	—	—	0	0	—	—	
" 17	80	20	8	—	—	—	—	—	—	0	0	—	—	
" 18		20	10	—	—	—	—	—	—	0	0	—	—	
" 19	81	20	7	—	—	—	—	—	—	0	0	—	—	
" 20		20	10	—	—	—	.136	—	—	0	0	—	—	
" 21	81	20	12	—	—	—	—	—	—	0	0	—	—	
" 22		20	10	—	—	—	—	—	—	0	0	—	—	
" 23	79	20	14	—	—	—	—	—	—	0	0	—	—	
" 24		20	13	—	—	—	.142	—	3440	0	0	3.6	—	
" 25	80	20	—	—	—	—	—	—	2700	0	0	3.6	—	
" 26		fast		—	—	—	—	—	1930	0	0	2.7	—	
" 27	79	fast		—	—	—	.120	—	2230	0	0	3.1	—	
" 28		fast		—	—	—	—	—	2070	0	0	2.8	—	
" 29	79	fast		—	—	—	—	—	2770	0	0	2.8	—	
" 30		fast		—	—	—	—	—	2810	0	0	2.5	—	
" 31	80	—	100	—	—	—	.091	—	2250	0	0	2.2	—	
April 1		—	100	—	—	—	—	—	3270	0	0	2.3	—	
" 2	79	—	100	—	—	900	—	—	2430	0	0	1.9	—	
" 3		—	100	—	—	900	—	—	1850	0	0	2.0	—	
" 4	77	—	100	—	—	900	.125	—	2220	0	0	3.9	—	
" 5		—	100	—	—	900	—	—	2280	0	0	4.1	—	
" 6	77	—	100	—	—	900	—	—	2550	—	—	2.5	—	
" 7		—	100	—	—	900	.124	—	2900	—	—	3.2	—	
" 8	77	25	100	—	—	1000	—	—	2120	0	0	3.4	—	
" 9		25	100	—	—	1000	—	—	2210	0	0	2.7	—	
" 10	76	25	100	—	—	1000	—	—	2200	0	ft.	2.8	—	
" 11		25	100	—	—	1000	.102	—	2450	0	0	3.4	—	
" 12	78	25	100	—	—	1000	—	—	2380	0	0	3.6	—	
" 13		25	100	—	—	1000	—	—	2190	0	0	3.3	—	
" 14	81	25	100	—	—	1000	—	—	2220	0	0	3.4	—	
" 15		25	100	—	—	1000	.102	—	2220	—	—	3.6	—	
" 16	80	25	200	—	—	1900	—	—	3260	—	—	5.4	—	
" 17		25	200	—	—	1900	—	—	2220	0	ft.	3.7	—	
" 18	80	25	200	—	—	1900	—	—	2500	0	0	2.1	—	
" 19		25	200	—	—	1900	—	—	2840	0	ft.	3.1	—	
" 20	81	25	200	—	—	1900	.139	—	2960	0	0	3.8	—	
" 21		25	200	—	—	1900	—	—	2260	0	0	3.9	—	
" 22	82	25	200	—	—	1900	.120	—	2510	0	0	3.8	—	
" 23		25	200	—	—	1900	.103	—	2380	0	0	3.8	—	

Note: ft. = faint

TABLE III. (*Continued*).

Date 1922	Weight lb.	DIET					BLOOD		URINE				Acetone 24 hrs. gm.
		Protein gm.	Fat gm.	Cll. gm.	Na Cl gm.	Total Calories	Plasma sugar mg. per 100cc.	Blood urea mg. per 100cc.	Volume cc.	Qualitative Dextrose	Nitro Prusside reaction	Total Nitrogen gm.	
" 24	82	25	200	—	—	1900	—	—	2320	0	ft.	3.2	—
" 25		25	200	—	—	1900	—	—	2270	0	0	3.8	—
" 26	82	25	200	—	—	—	.157	—	2070	0	0	3.9	—
" 27		25	200	—	—	—	—	—	2340	0	0	3.0	—
" 28	83	25	200	—	—	—	.133	—	2230	0	0	3.6	—
" 29		25	200	—	—	1900	—	—	2440	0	0	3.4	—
April 30	83	25	200	—	—	1900	.120	—	2310	0	ft.	2.4	—
May 1		25	200	—	—	1900	—	—	1830	0	0	3.4	—
" 2		25	200	—	—	1900	—	—	—	0	0	4.1	—
" 3		25	200	—	—	1900	.123	—	2230	0	0	3.9	—
" 4	82	25	200	—	—	1900	—	—	2570	0	0	3.9	—
" 5		25	200	—	—	1900	—	—	2430	0	ft.	3.6	—
" 6	80	25	200	—	—	1900	—	—	2270	0	0	3.1	—
" 7		25	200	—	—	1900	—	—	2340	0	0	3.4	—
" 8	80	25	200	—	—	1900	—	—	2000	0	0	3.0	—
" 9		25	200	—	—	1900	.137	—	2360	0	0	3.2	—
" 10	79	25	200	—	—	1900	—	—	2340	0	0	3.6	—
" 11		25	200	—	—	1900	—	—	2620	0	ft.	4.4	—
" 12	77	25	200	—	—	1900	—	—	2100	0	ft.	4.4	—
" 13		25	200	—	—	1900	.097	—	1950	0	ft.	4.3	—
" 14	78	25	200	—	—	1900	—	—	1930	0	ft.	4.5	—
" 15		35	200	5	—	1960	.166	—	2080	0	ft.	4.4	—
" 16	80	35	200	5	—	1960	—	—	2430	0	ft.	5.2	—
" 17		35	200	5	—	1960	—	—	1820	0	ft.	4.5	—
" 18	79	35	200	5	—	1960	—	—	2400	0	ft.	4.9	—
" 19		35	200	5	—	1960	.133	—	2240	0	ft.	6.6	—
" 20	79	35	200	5	—	1960	—	—	2330	0	0	5.8	—
" 21		35	200	5	—	1960	.135	—	2310	0	ft.	6.1	—
" 22	79	35	200	5	—	1960	—	—	2310	0	ft.	5.8	—
" 23		35	200	5	—	1960	—	—	2350	0	ft.	6.1	—
" 24	79	35	200	5	—	1960	—	—	2400	0	ft.	6.0	—
" 25		35	200	5	—	1960	—	—	2550	0	ft.	6.8	—
" 26	80	35	200	5	—	1960	.168	—	2330	0	ft.	3.4	—
" 27		35	200	5	—	1960	—	—	2010	0	ft.	4.4	—
" 28	80	35	200	5	—	1960	—	—	2200	0	0	3.8	1.3
" 29		35	200	5	—	1960	—	—	2400	0	ft.	3.6	1.3
" 30	80	35	200	5	—	1960	—	—	1950	0	0	4.1	5.4
" 31		35	200	5	—	1960	.166	—	2210	0	ft.	3.7	2.9
June 1	80	35	200	5	—	1960	—	—	1850	0	0	4.8	0.2
" 2		35	200	5	—	1960	—	—	1400	0	0	2.0	0.3
" 3	83	35	200	5	—	1960	.180	—	2670	0	0	5.3	1.6
" 4		35	200	5	—	1960	—	—	2300	0	0	4.8	1.3
" 5	83	35	200	5	—	1960	—	—	2660	—	—	4.2	1.3
" 6		35	200	5	—	1960	—	—	2530	—	—	3.5	1.3
" 7	84	35	200	5	—	1960	.200	—	3020	—	—	4.3	5.4
" 8		35	200	5	—	1960	—	—	3320	—	—	5.1	2.9
" 9	83	35	200	5	2	1960	—	—	2820	—	—	4.3	0.248
" 10		35	200	5	2	1960	—	—	3100	—	—	4.9	0.327

TABLE III. (*Continued*).

Date 1922		Weight lb.	DIET					BLOOD		URINE					Acetone 24 hrs. gm.
			Protein gm.	Fat gm.	CH gm.	Na Cl gm.	Total Calories	Plasma sugar mg. per 100 cc.	Blood urea mg. per 100 cc.	Volume cc.	Qualitative Dextrose	Nitro Prusside reaction	Total Nitrogen gm.		
"	11	83	35	200	5	2	1960	.156	—	3030	—	—	4.1		0.916
"	12		35	200	5	2	1960	—	—		—	—	—		0.632
"	13	82	35	200	5	2	1960	—	—	3200	—	—	4.9		0.148
"	14		35	200	5	2	1960	—	—	2040	—	—	3.1		0.400
"	15	85	35	200	5	2	1960	—	—	2620	—	—	3.3		—
"	16		35	200	5	2	1960	.175	—	2430	—	—	5.2		—
"	17	86	35	200	5	2	1960	—	—	1820	—	—	4.5		—
"	18		35	200	5	2	1960	—	—	2400	—	—	4.5		—
"	19	84	35	200	5	2	1960	—	—	2510	—	—	6.6		—
"	20		35	200	5	2	1960	.180	—	2240	0	0	5.8		—
"	21	85	35	200	5	2	1960	—	—	2330	0	—	6.1		—
"	22		35	200	5	2	1960	—	—	2310	—	—	5.8		—
"	23	84	35	200	5	2	1960	.226	—	2350	—	—	6.1		—
"	24		35	200	5	2	1960	—	—	2400	—	—	6.0		—
"	25	84	35	1	25	2	249	—	—	2800	0	0	5.5		0.120
"	26		35	1	25	2	249	—	—	2380	0	0	6.0		—
"	27	84	35	1	25	2	249	—	—	3080	0	0	5.7		—
"	28		35	2	25	2	258	—	—	3110	0	0	5.4		—
"	29	83	35	1	25	2	249	.203	—	2140	0	0	5.0		—
"	30		35	2	25	2	258	—	—	2980	0	0	4.3		—
July	1	84	35	1	25	2	259	—	—	3570	0	0	3.5		—
"	2		35	15	5	2	295	—	—	2960	0	0	5.2		—
"	3	84	35	11	5	2	193	—	—	2150	0	0	6.0		—
"	4		35	14	5	2	286	.184	—	2900	0	0	7.3		—
"	5	82	35		5	—	160	—	—	3200	0	0	6.4		—
"	6		35	11	5	2	259	—	—	2980	0	0	3.1		—
"	7	84	35	13	5	2	277	—	—	3460	0	0	5.8		—
"	8		35	13	5	2	277	.195	—	3290	0	0	5.9		—
"	9	84	35	12	5	2	268	—	—	2460	0	0	4.3		—
"	10		35	11	5	2	259	—	—	3320	0	0	5.3		—
"	11	83	35	14	5	2	286	—	—	3170	0	0	5.7		—
"	12		35	15	5	2	295	.128	—	2800	0	0	5.9		—

Note: ft. = faint

admitted to the Physiatric Institute March 6, 1920. The physical examination was negative except for emaciation. With a height of 5 feet 4 inches, her highest weight had been 128 pounds, and the weight at admission was 102 pounds.

The existing glycosuria and ketonuria were rather easily controlled by the usual semi-starvation period, and the diet was readily built up to 1500 calories, with normal blood sugar. The patient was discharged in this condition April 17, 1920. She was again in the Institute from October 18, 1920 to June 9, 1921, and from February 8, 1922 to August 22, 1922. These readmissions were made necessary by persistent slight violations of diet on her part. Office examinations

in the interval were made unreliable through the patient's trick of habitually taking extra food, and then preparing herself by fasting or greatly reduced diet for several days in advance of a blood analysis. The gradual loss of tolerance thus produced reached a considerable degree before this deception was discovered, and the repeated reductions of diet for clearing up hyperglycemia resulted in loss of weight. The experimental data of the present study are contained in Table III.

Entering on Feb. 7, with glycosuria and ketonuria present, the patient was placed on a diet of 30 gm. protein. Glycosuria ceased on Feb. 10, and the first blood sample was taken and showed plasma sugar of 0.500 per cent., illustrating a very high renal threshold for sugar. On the same diet, the plasma sugar by Feb. 13 had fallen to 0.385 per cent. A program was then begun of alternate days of 20 gm. of protein, with complete fasting on the intervening days. This program, continued to March 7, reduced the plasma sugar to 0.195 per cent. Though the case had been of a relatively mild and unprogressive type, this stubborness of the blood sugar indicated that it had reached a severe stage. The body weight had been 81 pounds at admission, and on March 7 was still 82 pounds, on a salt-poor diet without visible edema.

Diets of first 10 and then 20 gm. of protein per day further reduced the plasma sugar but failed to bring it thoroughly to normal. Accordingly, a 5-day period of complete fasting was imposed, March 26 to 30, and the plasma sugar was thus brought to the fully normal level of 0.091 per cent. The body weight was 80 pounds, and the patient, though weaker than at admission, had no serious complaint and was able to take walks of considerable length.

March 31 to April 7 inclusive, the only food given consisted of 100 gm. of fat daily in the form of butter or olive oil. The plasma sugar ran slightly higher, namely at 0.125 and 0.121 per cent., but the absence of real hyperglycemia corresponds to the usual experience on pure fat feeding.

April 8 to 15, the diet was 25 gm. protein and 100 gm. fat. On this ration of 1000 calories the plasma sugar held the normal level of 0.102 per cent.

April 16 to May 11, the allowance of 25 gm. protein was continued, while the fat was increased to 200 gm. daily. This ration of 1900 calories was higher in energy value than anything the patient had ever previously tolerated. The blood sugars fluctuated at first; though there was a rise to 0.157 per cent.

on April 26, there was a subsequent fall to 0.120 per cent. on April 30 and to 0.097 per cent on May 13. The body weight, instead of rising, fell a trifle (77-78 pounds, May 12-14), though it is to be assumed that some tissue had actually been gained and that the fat had merely driven out water. Acidosis remained absent, as judged by normal CO_2 capacity of the plasma (never below 58.6 volume per cent.) and negative or trivial nitroprusside reactions in the urine. The patient for the first week was strengthened by the high fat diet. Thereafter she made increasing complaints of weakness and general malaise, to a greater degree than at any time in the preceding period of extreme privation. Though the diet kitchen had succeded in preparing the food so that it was taken continuously without repugnance, the above complaints finally necessitated a change to a better balanced diet.

Accordingly, May 15 to June 24 the diet consisted of 35 gm. protein, 5 gm. carbohydrate and 1960 calories. The appetite and digestion remained good, and the complaints of weakness and malaise, though persistent, were less. There was evidently gain of both tissue and weight, and at the end of this period the patient weighed 84 pounds. Glycosuria and ketonuria remained absent, but the plasma sugar showed an irregularly rising tendency, and at the end of this period it was 0.226 per cent.

June 25 to July 1, the patient was changed to a lower caloric ration with the same theoretical glucose value. Reckoning the potential carbohydrate in the form of glycerol as 10 per cent. of the weight of fat, the 200 gm. of fat in the former diet was equivalent to 20 gm. of carbohydrate. Therefore, keeping the protein unchanged the diet was made practically fat-free, and the carbohydrate was increased by 20 gm., making 25 gm. daily. The plasma sugar by June 30 thus declined to 0.203 per cent. A further slow decline would probably have continued, but circumstances required terminating the experiment within a comparatively short time.

July 2 to 12, the carbohydrate was reduced to 5 gm. daily, so that the diet was identical with that during the high caloric period except for the omission of 200 gm. of fat. This change was made in the patient's interest, in order to reduce the blood sugar within the time available. The sharp reduction of calories is so powerful in its influence that it would probably

have brought the blood sugar down gradually, even under the handicap of 25 gm. of carbohydrate. Nothing in the known facts of metabolism, however, requires such a handicap in such an experiment. Under the established laws of fat metabolism, the feeding of 200 gm. of fat would increase actual fat combustion only slightly. On the other hand, the sparing action of the fat should theoretically reduce protein catabolism slightly, and such a reduction is indicated by the urinary nitrogen, which averaged 4.31 gm. daily during the period April 15 to June 24, a daily average balance of 0.17 gm. for this period, estimating fecal nitrogen as one-twelfth of the total food nitrogen, and 5.53 daily during the period July 2 to 12, with a balance of 0.46 gm. No proof therefore exists that the quantity of glucose in combustion was reduced in a manner to explain the powerful influence of fat omission upon the plasma sugar, which by July 12 had fallen to 0.128 per cent.

It was necessary to break off the experiment at this point. The patient at home now tolerates a diet of 50 gm. protein, 10 gm. carbohydrate and 1000 calories. Under favorable conditions this tolerance can be slightly increased, but it is a safe prediction that stealing of fat or any other food will entail further downward progress.

Two points in this experiment require special mention. First, the nitrogen balances for the different periods were as follows:

DATE	Average daily N intake gm.	Average daily N output gm.	Estimated fecal N (one-twelfth of food N)	Total N.	N. Bal.
April 15 to May 15	4.00	3.64	.33	3.97	+.03
May 15 to June 24	5.60	4.86	.46	5.33	+.27
July 2 to July 12	5.60	5.53	.46	5.99	—.39

It is usual for patients to lose quantities of body nitrogen, in proportion to the severity of their diabetes, during the initial period of privation which brings their symptoms under control. Though unfortunate in some respects, this loss is more than balanced by the benefit resulting from control of the diabetes, and in our experience a lasting benefit is not otherwise obtainable in severe cases.

Second, the influence of fat feeding is quickly demonstrable in cases which are sufficiently severe and progressive in type. Though this case represented diabetes in a severe stage in a young person, the history showed that it was less rapidly progressive with errors of diet than most cases at this age. The effect of fat is therefore easily missed unless the tests are sufficiently accurate and prolonged. The variations in blood sugar may be regarded as accidental, and the cases may be classified merely as "not responding satisfactorily to treatment", as was done by Newburgh and Marsh with some of their cases. The general fact can still be demonstrated that the blood sugar rises on excessive caloric diets and can be kept normal only by limitation of the total calories and body weight.

Conclusions.

Observations on three patients are here reported, showing the effect of increasing the diet with fat beyond the caloric tolerance. Injury of the assimilation is manifested by a rise of blood sugar, which is generally slow but in the severest cases may be rapid. These is agreement with Newburgh and Marsh in the belief that the blood sugar should be kept normal, especially in young patients, and that glycosuria and other harmful symptoms result if hyperglycemia is ignored. There is disagreement with the view of Newburgh and Marsh that this result can be achieved, especially in severe cases, without restriction of fat, total calories and body weight.

These cases illustrate the well known fact that in fasting or under-nutrition, even emaciated patients derive their energy chiefly from body fat. It is known that such patients maintain a low level of total and nitrogeneous metabolism. Excessive nitrogen elimination, such as observed by Joslin, may be classed with the familiar premortal rise of nitrogen in starved animals, but it is easy to show that even in this final stage the blood sugar is reduced by undernutrition and raised by high fat diets. None of the facts, therefore, warrant an assumption that high fat diets will suppress hyperglycemia or glycosuria by means of a marked reduction of protein catabolism. The statement that severe cases of diabetes which are resistant to undernutrition or fasting can be cleared up by high fat diets is contrary to all experience in this Institute

and in our opinion also contrary to fact. All the observations here have conformed to the opposite rule, as illustrated in these three cases.

There is a strong recent tendency to regard metabolism solely in terms of glucose and fatty acids burned, and thus to infer that the effects upon diabetes are the same whether these substances are derived from the food or from the bodily stores. It should be clearly understood that this inference is purely speculative, and it is unsound because it ignores the other element involved in diabetes, namely the internal secretion of the pancreas. An abundance of animal and clinical experiments have been published from this Institute and from the Rockefeller Institute proving that reduction of total diet and body weight reduces the strain upon the internal pancreatic function, and increase of diet and body weight increases the strain upon this function. The attempt to prevent undernutrition by giving fat or any other kind of food prevents also the benefits of undernutrition. This matter is one of fact, not theory. It is desirable that accurate experiments of this kind be repeated by as many observers as possible, in order to correct prevalent errors and settle the point beyond dispute.

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A STUDY OF METABOLISM IN CHLOROFORM POISONING.

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In the work of Graham[1] on late poisoning with chloroform and other alkyl halides, a theory was advanced to clear up the mystery of delayed chloroform poisoning and to explain adequately the cause of the lesions produced.

From the chemical formula —

$$CHCl_3 + O \qquad COCl_2 + HCl$$
$$COCl_2 + HOH \qquad CO_2 + 2HCl$$

Graham draws the conclusion that three molecules of HCl are formed in the body from each molecule of $HCCl_3$ in the presence of water by oxidation. The presence of the acid formed is the cause for the necrosis produced, more especially in the liver since this is the site of a most active metabolism.

The following are the more important of the studies undertaken to prove this theory —

1. Morphological changes produced by HCl especially in the liver.
2. The demonstration of free HCl in the necrotic areas of the liver.
3. The inhibiting effect of alkali.
4. Necrotic power of various chlorine derivatives of methane (as dichlor and tetrachlormethane).
5. Production of the same lesions with bromoform and iodoform.
6. The effect of alkyl halides in general.
7. Study of the comparative action of choral hydrate to $HCCl_3$.

In reviewing the conclusions derived from his series of studies several prominent features are brought to light which tend to cast doubt upon the HCl theory.

* The data are from the thesis of Dr. Robert Kapsinow presented in candidacy for the degree of Doctor of Medicine, Yale University, 1922.

Oral and intraportal administrations of HCl are followed by certain changes characteristic of necrosis. Graham injects intraportally in dogs a relatively high concentration of HCl, 10-25 cc. of a 0.5-1 per cent. solution, and produces extensive peripheral necrosis in the liver. The observation is undoubtedly correct but to interpret from this that HCl is formed from $HCCl_3$ and that this is the cause of the necrosis may rightly be questioned. It will be recognized that the concentration of HCl used was stronger than that found in the stomach where the greatest acidity of the body is present. This concentration is strong enough to modify the character of protein. This is in agreement with his observation that when HCl is injected intraportally peripheral necrosis develops, which he says, is to be expected, since the peripheral would be the first part of the lobule to be reached by the acid, because of the arrangement of the blood supply. This is contrary to pathological facts of chloroform poisoning but rather coincides with the idea that the acid modifies the blood in the periphery and hence causes inanition necrosis.

His attempt to demonstrate free H ions and free chlorine ions in the necrotic tissue has little significance since it is probable that they may be present in all necrotic tissue.

Having formulated this HCl theory, Graham next demonstrated that the administration of alkali simultaneously with $HCCl_3$ would inhibit if not absolutely prevent the occurrence of necrosis. The method used was to give 17 gm. $Na_2CO_3.10H_2O$ in 1700 cc. of a 1.4 per cent. NaCl solution intravenously during the anesthesia. The result was that the animals showed fewer pathological lesions.

Davis and Whipple[2] have been unable to corroborate Graham's conclusions. They offer the further suggestion that it is no more difficult to explain $HCCl_3$ necrosis than to explain how and why the $HCCl_3$ passes by all tissues until it reaches the liver where this hypothetical reaction takes place with the liberation of HCl.

The next observation made by Graham is that $HCCl_3$ and $HCBr_3$ produce the same type of necrosis as does $HCCl_3$ and he demonstrates the presence of free ions in the necrotic area by neutral red, obtaining the same results as with $HCCl_3$. Neutral red does not identify free bromine or iodine ions but the presence of an acid medium, hence this observation is not con-

clusive inasmuch as necrotic tissue may contain acid reacting bodies[3].

In considering the various chlorine derivatives of methane such as dichlormethane and tetrachlormethane, Graham finds that these have the power to produce central necrosis in the liver as does $HCCl_3$, but that the necrosis is proportional to the amount of HCl which can be theoretically formed. When one considers the reference he quotes, with regard to the high degree of temperature necessary to hydrolyze CCl_4 to four molecules of HCl and to convert H_2CCl_2 to two molecules of HCl, it is difficult to see where in the human body such a reaction would necessarily be applicable.

The lesions that are produced by chloral hydrate are dependent upon the amount of substance given. To compare the relative extent of tissue change produced by chloral hydrate and chloroform upon the basis of chlorine ions, equivalent amounts should be taken. Graham does not describe the amount of chloral hydrate given which may have been too small to have caused any lesion, for Cushny[4] states that the effects of chloral on tissue change corresponds very closely to those of chloroform. Thus fatty degeneration of various organs has been produced by prolonged administration of chloral and chloralamide.

From the foregoing discussion it appears that more evidence must be offered before the HCl theory can be accepted. For this purpose a study of the metabolic changes produced by delayed chloroform poisoning has been undertaken.

Method

The animals used were adult rabbits since it has been demonstrated by Underhill[5] that the urine of normal starving rabbits shows a reduction to zero or a trace in the chloride content usually after the third day of starvation. If $HCCl_3$ did form HCl it was expected that there would therefore be a rise in the output of chlorides. The urine was collected for 24-hour periods and analyzed for chloride, phosphate, creatine, creatinine, and total nitrogen. Distilled water was given *ad libitum*. Squibb's chloroform was used, the dosage being 1 cc. dissolved in 1 cc. olive oil per kilo body weight, injected subcutananeously.

The methods of analysis for the above substances were

those described and compiled by Underhill in the "Manual of Selected Biochemical Methods".

Chlorides—The method of Volhard-Arnold.

Phosphates—Uranium acetate method.

Creatinine—Folin's colorimetric method.

Creatine—Folin-Benedict method.

Total Nitrogen—Kjeldahl method.

The investigation was planned to include several viewpoints.

1. A study of the excretion of chlorides, phosphates, creatinine, creatine and total nitrogen in normal starving rabbits.

2. The effect of chloroform on the excretion in the urine of these substances.

3. The influence of anesthesia alone.

4. The effect of an injection of an amount of chloride, as NaCl, equivalent to that contained in the amount of HCC_3. introduced.

5. The influence of anaesthesia followed by the introduction of the above equivalent amount of NaCl.

6. The effect of anesthesia followed by the usual dosage of $HCCl_3$.

7. A study of alkali as an inhibiting agent to $HCCl_3$ poisoning.

In all the above studies the main emphasis has been laid on the chloride content of the urine.

The Study of the Urine of Normal Starving Rabbits

The analyses of the urine of about 30 starving rabbits showed the following results: (see Table I for typical findings).

(a) The chloride content is highest the first day of starvation. This is followed usually by a marked reduction on the second day and on the third and fourth day the excretion may be zero or a trace only. On the fifth day there may be a slight rise which may be somewhat variable. The chlorides may reach zero on the third day and then rise to about 45-60 milligrams or they may only drop to about 30 milligrams, but remain with this as a minimum level from which they may rise on the fourth or fifth day.

(b) The phosphate excretion reaches its highest point at

the third day and then gradually approaches the same level as at the beginning of starvation.

TABLE I

Composition of the Urine of Normal Rabbits without Food

Rabbit AA

Date	Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921	cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
June 2	200	190	.150	.150	86.1	1.8	.150
" 3	200	190	.060	.175	80.1	21.1	.570
" 4	185	150	.060	.200	73.6	27.5	.600
" 5	200	160	.060	.175	74.3	23.2	.615
" 6	200	180	.090	.150	62.7	23.4	.690

Rabbit Z

May 21	30	30	.030	.100	86.1	6.9	.450
" 22	50	20	.015	.125	82.6	5.1	.660
" 23	60	28	.000	.225	81.0	7.0	lost
" 24	80	30	.030	.188	69.2	11.7	.885

Rabbit H

Jan. 6	400	500	.135	.275	89.0	14.8	.270
" 7	600	575	.104	.315	86.0	17.7	.690
" 8	600	515	.097	.340	82.6	25.6	.727
" 9	520	430	.090	.237	63.7	26.7	.826
" 10	280	210	.075	.262	62.3	38.9	.795
" 11	290	155	.060	.225	40.9	45.2	.855

(c) The creatinine in all cases showed a decided reduction thruout.

(d) Creatine which is formed in slight amounts on the first day of starvation is readily poured out as inanition continues. (These results coincide with the observations of Rose[5a] and Underhill[6] on the effect of inanition on the excretion of creatinine and creatine).

(e) The total nitrogen increases up to a maximum point as shown by Rabbits AA and H in Table I. This increase seems to be parallel to the increase in creatine.

The Effect of the Injection of $HCCl_3$ on the Urinary Constituents

A series of rabbits were starved for a period of 3 and 4 days. They were then injected subcutaneously with Squibb's chloroform for anesthesia. The dosage used was 1 cc. in 1 cc. of olive oil per kilo body weight. Table II demonstrates definitely the effect of $HCCl_3$ upon the chloride content of the urine.

The chlorides in no case show any marked change from the normal starving rabbit. It was assumed that if Graham's HCl theory were correct, there should be an increase in the chloride output. This is demonstrated best in Table IIa.

The other constituents of the urine do not show any marked change from those of the normal starving condition.

From this study alone it is quite definite that there is no evidence for the formation of chlorides from $HCCl_3$ otherwise the chloride content of the urine should show some alteration from the normal curve.

TABLE II

The Influence of Chloroform upon the Composition of the Urine

Rabbit T—Wt. 1400 gms.

Dose — 1 cc. $HCCl_3$ + 1 cc. oil per kilo.

Date		Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921		cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
Apr.	27	75	98	.300	.210	58.6	4.5	.795
"	28	200	230	.210	.250	52.2	43.0	.793
"	29	75	65	.000	.275	47.3	53.6	.990
"	30*	55	45	.090	.300	50.0	60.9	1.320
May	1	115	76	.045	.560	42.8	92.1	1.470

Rabbit U—Wt. 1380 gms.

Dose — 1 cc. $HCCl_3$ + 1 cc. oil per kilo.

May	2	225	52	.000	.125	74.3	9.1	.450
"	3	80	52	.000	.175	57.4	34.6	.720
"	4	75	40	.000	.225	48.2	47.0	.855
"	5*	100	40	.000	.225	42.6	41.7	.900
"	6	145	20	.000	.150	18.8	22.1	.285

Rabbit V—Wt. 2000 gms.
Dose — 1 cc. $HCCl_3$ + 1 cc. oil per kilo.

May	7	50	40	.060	.400	84.3	10.9	.885
"	8	70	30	.000	.375	86.1	3.8	.900
"	9	75	28	.000	.300	81.0	9.0	.860
"	10*	75	34	.000	.263	77.1	14.9	.780
"	11	200	70	Trace	.100	69.8	12.8	.540

* Day of Injection.

TABLE IIa

The Influence of Chloroform upon the Excretion of Urinary Chlorides

Rabbit T

Date	Water Intake	Urine Output	Chlorides
1921	cc.	cc.	gm.
Apr. 27	75	90	.300
" 28	200	230	.210
" 29	75	65	.000
" 30*	55	45	.090
May 1	115	76	.045

* Injected 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 1400 gms.

Rabbit U

Date	Water Intake	Urine Output	Chlorides
1921	cc.	cc.	gm.
May 2	225	52	.000
" 3	80	52	.000
" 4	75	40	.000
" 5*	100	40	.000
" 6	145	20	.000

* Injected 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 1380 gms.

Rabbit V

May	7	50	40	.060
"	8	70	30	.000
9	9	75	28	.000
"	10*	75	34	.000
"	11	200	70	trace

* Injected 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 2000 gms.

Rabbit W

May	12	220	60	.030
"	13	60	68	.000
"	14*	100	90	.000
"	15	190	110	.030

* Injected 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 1900 gms.

Rabbit X

May	26	200	170	.060
"	27	200	250	.000
"	28*	200	170	.000
"	29	50	50	.060

* Injected 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 1900 gms.

Rabbit Z

May	30	80	35	.090
"	31	40	30	.030
June	1*	35	24	.030
"	2	40	42	.030

* Injected 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 1850 gms.

The Effect of simple Anesthesia on the Urinary Constituents

The next step was to study the effect that anesthesia alone might have upon the excretion of chlorides. For this purpose Squibb's ether for anesthesia was used. The dosage employed in this series was 5 cc. ether and 1 cc. oil per kilo.

Some animals were only given one injection in the morning

and others given two injections, one in the morning and one in the evening, to produce a longer period of anaesthesia.

Table IIIa shows the effect after only one injection of ether. Table IIIb demonstrates the influence of two injections. In the former, altho the basic level for chloride excretion was high still the introduction of ether had no marked effect upon the chloride output. Likewise Table IIIb shows that following two injections the chloride content does not differ greatly from either the normal starving urine or the chloroform urine of Table IIa. The other constituents do not show any material difference from the normal starving condition except for a rather high creatine content.

The Effect of NaCl on the Urinary Constituents

In this series of experiments the object was to inject subcutaneously that amount of chloride as NaCl equivalent to the chlorine content of $HCCl_3$ in order to determine whether if chlorides were formed they would be excreted in sufficient quantity to be detected.

Table IV definitely shows that when amounts of chlorides equivalent to that contained in the chloroform injected are introduced the chloride output is increased markedly. It seems quite conclusive that if $HCCl_3$, did form HCl there should be a definite change in the chloride content of the

TABLE IIIa

The Influence of Anesthesia by Ether upon Urinary Composition

Rabbit II

Date	Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921	cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
Jan. 19	300	370	.288	.310	67.6	12.3	.604
" 20	700	600	.216	.360	68.4	25.8	.828
" 21	500	455	.210	.375	68.6	26.6	.960
" 22*	600	520	.198	.385	72.4	17.6	1.056
" 23	500	380	.192	.360	65.5	40.7	.912

* Injected 5 cc. ether + 1 cc. oil per kilo. Wt. 2440 gms.

TABLE IIIb

The Influence of Anesthesia by Ether upon Urinary Composition

Rabbit E

Date		Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921		cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
Jan.	12	100	60	.150	.200	37.8	1.8	.765
"	13	100	30	.120	.260	33.7	8.8	.660
"	14	100	26	.072	.280	39.0	22.1	.678
"	15*	100	21	.084	.240	27.2	10.8	.600
"	16x	100	24	.048	.140	24.6	59.8	.648
"	17	100	25	.072	.140	32.40	52.84	.720

* Injected 5 cc. ether + 1 cc. oil per kilo. Wt. 1250 gms.
x Injected 5 cc. ether + 1 cc. oil per kilo { 8:30 A.M. / 4:00 P.M.

TABLE IV

The Influence of Sodium Chloride Injection upon Urinary Composition

Rabbit 3A

Date		Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921		cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
June	11	60	130	.165	.163	97.8	3.7	.600
"	12	50	170	.090	.175	71.0	10.0	.600
"	13*	190	150	.165	.250	67.5	12.6	.750
"	14	320	130	.880	.225	75.7	36.8	.750

* Injected 3.74 gm. NaCl in 5 per cent. solution. Wt. 1700 gms.

Rabbit 2B

June	11	10	25	.150	.163	69.2	10.1	.540
"	12	40	60	.075	.225	68.7	12.0	.660
"	13*	40	28	.075	.163	48.2	9.6	.720
"	14	340	250	1.800	.200	64.8	11.6	.720
"	15	70	105	.406	.150	80.1	88.5	1.005

* Injected 4.07 gm. NaCl in 5 per cent. solution. Wt. 1850 gms.

urine. There is also a marked increase in the creatinine and creatine content. Not all the chloride was recovered at the end of the first day, perhaps because the solution injected was rather concentrated.

The Effect of Anesthesia Followed by NaCl

A question arose next as to whether anesthesia had any effect upon the excretion of chlorides, in other words, would

the anesthesia prevent the excretion of chlorides if they were formed from $HCCl_3$. In this series ether was used as in the previous experiments with the 5 cc. per kilo dosage. After 24 hours NaCl equivalent in chlorine content to the dose of $HCCl_3$ employed was introduced.

Table V illustrates the influence of the combined factors of anaesthesia plus increase in chloride introduction. It seems to us that this should be the picture that $HCCl_3$ ought to have illustrated if the HCl theory were correct. The same findings are present following the introduction of ether and saline as occurs with each alone. Following the ether administration, the chlorides are not affected but there is a high increase in creatine output with a slight rise in creatinine. Subsequent to the chloride injection, the chloride output is greatly increased and the creatinine and creatine are still high.

The Effect of Anesthesia Followed by $HCCl_3$

The following series was carried through in order to study the effect of anesthesia prior to $HCCl_3$ injection, thereby comparing the action of ether and chloroform upon the chloride content of the urine and incidentally noting the others.

TABLE V

The Influence of Ether and Sodium Chloride Injection upon Urinary Composition

Rabbit 5A

Date		Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921		cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
June	21	100	30	.030	.125	65.8	12.0	.420
"	22	200	170	.030	.150	49.0	39.0	.660
"	23*	200	210	.045	.150	46.0	33.3	.660
"	24x	350	250	.059	.260	59.1	128.8	.837
"	25	330	300	2.100	.525	59.9	46.5	.672

* Injected with 4 cc. ether + 1 cc. oil per kilo at 8:00 A.M. Wt. 1770 gms.
Injected with 4 cc. ether + 1 cc. oil per kilo at 7:00 P.M.
x Injected with NaCl 2.2 gm. per kilo.

On examining the chloride output, as demonstrated in Table VI, one sees that the narcotic factor plays no particular rôle on the chloride mechanism, indicating thereby that even tho an attempt was made to upset the normal picture by a

previous period of anesthesia, the chloride output is not altered. It seems quite clear that if $HCCl_3$ did form HCl, at least part of it ought to be excreted in an amount that could be detected in spite of the possibility of very early pathological conditions.

It is also noted that the ether has the same effect on creatine as in the previous experiments.

The Influence of an Alkaline Diet as a Possible Inhibitory Agent to $HCCl_3$ Poisoning

In order to determine still further the possibility of the conversion of $HCCl_3$ into HCl and to confirm the inhibitory action that the administration of alkali may have on $HCCl_3$ poisoning as described by Graham, the animals were put on diets yielding a basic ash.

A liberal quantity of fresh carrots (200 gms.) was fed to the animals for a period of 3 and 6 days prior to the injection of $HCCl_3$.

In two cases, Rabbits O and N (see Table VIIa), died 34-36 hours after the injection of $HCCl_3$. Rabbit P lived only 2 days after the injection. Rabbit Q was alive until the end of the experiment. From this observation alone we would say that alkali had no effect upon the inhibition of $HCCl_3$ poisoning.

The use of a carrot diet is perhaps a more logical way of alkalizing an animal than giving the animal intravenous alkaline solution as Graham has done, for even he asserts "that it is difficult to know the exact amount to give because

TABLE VI

The Influence of Ether and Chloroform upon Urinary Composition

Rabbit 4B

Date	Water Intake	Urine Output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921	cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
June 21	80	40	.060	.125	57.0	16.5	.420
" 22	70	60	.045	.225	63.2	33.1	.660
" 23*	80	100	.090	.225	59.1	37.3	.660
" 24x	160	150	.090	.825	58.2	89.0	.837
" 25	400	250	.120	.400	37.3	63.3	.678

Rabbit I

Jan.	25	150	65	.108	.240	53.0	13.0	.288
"	26	170	115	.084	.250	51.3	25.0	.396
"	27*	165	105	.096	.220	38.1	29.3	.564
"	28x	150	62	.120	.140	49.8	lost	.696
"	29	95	27	.096	.120	24.5	29.4	.828

* Injected with 4 cc. ether + 1 cc. oil per kilo at 8:00 A.M. and 7:00 P.M.
x Injected with 1 cc. $HCCl_3$ + 1 cc. oil per kilo.

TABLE VIIa

The Influence of an Alkaline Diet upon Urinary Composition in Chloroform Poisoning

Rabbit 0

Date	Carrots	Water Intake	Urine	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921	gm.	cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
Mar. 21	200	155	180	.204	.470	69.6	15.9	.636
" 22	200	85	190	.336	.330	79.0	12.2	.444
" 23*	200	60	208	.465	.463	88.0	19.9	.563
" 24	160	85	10	.108	.060	43.2	49.3	.396
Died								

* Injected with 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 2500 gms.

Rabbit N

Mar.	24	200	50	170	.204	.290	88.7	10.9	.396
"	25	200	200?	280	.180	.225	100.2	12.4	.558
"	26*	200	180	346	.252	.263	107.9	11.3	.558
"	27	200	200	114	.144	.180	60.5	7.6	.240
Died									

* Injected with 1 cc. $HCCl_3$ + 1 cc. oil per kilo. Wt. 2750 gms.

it was impossible to know how much acid would be liberated". The reports of his findings were that alkali injection failed to inhibit necrosis in one animal even tho the amount of alkali administered was excessive, but in the other animals the pathological findings were less severe. In his later paper[7] he reports "that absolute inhibition to $HCCl_3$ liver necrosis is not to be expected uniformly by the use of alkali as Na_2CO_3 for the reason that this substance gains entrance to the cell with difficulty".

In the three cases reported here in which the diet failed to inhibit poisoning, autopsy revealed in each instance severe fatty necrosis and it was difficult to note any alteration in severity from those of $HCCl_3$ on starving animals. In our opinion, alkali has no protective effect on $HCCl_3$ poisoning.

In only one case did an animal survive the $HCCl_3$ poisoning. The findings will be discussed separately.

Taking an average of the urinary constituents prior to the injection we find that in all cases there is a reduction of ⅓ to ½ in the chloride output. The phosphates are reduced to ½. The creatinine in two cases is reduced ½ and in the other two cases slightly increased. The total nitrogen follows the creatinine. The creatinine seems to have shown the most marked change of all being increased 3-1 times that of the average.

It seems from a study of this series that if $HCCl_3$ did form HCl there certainly was plenty of alkali available for neutralizing the acid as fast as it could be liberated, and appear as such in the urine.

The fact that an animal did live thru the period of poisoning gave us an opportunity to study the length of time it requires for the liver to return to normal and also the effect that absorption of the dead cells has upon the urinary constituents.

A study of Table VIIb, Rabbit Q, shows that the excretion of chlorides tends to follow the diet. Following the injection of $HCCl_3$ there is a reduction in the output of chlorides and at the same time an equal reduction in the food intake. As the animal recovers from the effect of the poisoning there is an increase in the output of chlorides and a simultaneous increase in the diet, both conditions returning to normal at the fifth day following the injection of $HCCl_3$. The table definitely indicates that there is neither an immediate nor a delayed increase in chloride output as a result of the injection. The phosphates follow a course almost parallel to that of the chlorides and the diet.

The most interesting part of this experiment is the course of the creatine, creatinine and total nitrogen. Following the injection of $HCCl_3$ there is an almost immediate rise in the output of the creatinine which reaches its maximum in height at the second day following the injection and then quickly returns to the normal level at the fifth day with the other substances. The creatine and total nitrogen rise to their maximum heights at the third day almost in parallel curves and as suddenly return to normal, altho the total nitrogen is somewhat delayed. It seems that the absorption of the dead liver cells which are rich in nitrogenous content,

reaches its maximum at the end of the third day and is almost completed at the end of the fifth day.

It is difficult to conclude positively that necrotic liver tissue is absorbed by the end of the third day and completely regenerated by the end of the fifth day.

Discussion

In reviewing the work of Graham on late poisoning following $HCCl_3$ and other alkyl halides, certain factors stand out most definitely in his attempt to explain the symptoms

TABLE VIIb

The Influence of an Alkaline Diet upon Urinary Composition in Chloroform Poisoning

Rabbit P

Date	Carrots	Water Intake	Urine output	Chlorides	Phosphates	Creatinine	Creatine	Total N
1921	gm.	cc.	cc.	gm.	gm.	mgm.	mgm.	gm.
Mar. 30	200	115	228	.345	.325	81.0	20.2	.825
" 31	200	85	182	.216	.340	80.0	18.7	.780
Apr. 1	200	85	180	.204	.300	81.0	14.2	.612
" 2	200	75	114	.180	.280	80.0	16.7	.576
" 3*	200	55	176	.240	.340	81.0	14.2	.600
" 4	200	65	112	.132	.460	73.8	46.2	.576
" 5	50	90	34	.120	.220	92.5	61.7	.900
	Died							

* Injected with 1 cc. $HCCl_3 + 1$ cc. oil per kilo.

Rabbit Q

Mar. 30	200	200	265 (some lost)	.306	.540	81.0	8.1	.900
" 31	200	140	180	.192	.280	64.8	11.4	.540
Apr. 1	200	140	225	.225	.525	82.6	12.6	.750
" 2	200	125	205	.300	.450	84.3	9.8	.630
" 3	200	110	208	lost	—	—	—	—
" 4*	200	135	190	.288	.360	68.9	11.4	.540
" 5	200	200	225	.135	.350	86.1	20.4	.675
" 6	105	200	150	.120	.225	109.4	27.8	.840
" 7	100	160	128	.105	.200	86.1	75.8	1.200
" 8	190	100	174	.345	.175	80.1	35.5	1.125
" 9	200	120	260	.360	.360	70.5	19.4	.825
	Living							

* Injected with 1 cc. $HCCl_3 + 1$ cc. oil per kilo.

resulting from chloroform poisoning as due to the liberation of HCl. The facts offered for this theory seem doubtful.

In repeating this study we find that by using rabbits whose chloride content in the urine is reduced to zero or a trace at the end of a starving period of three days, and injecting them with $HCCl_3$ there is no increase in the chloride output. Such an increase would be expected if the HCl theory were true. The next step was to see whether NaCl equivalent to $HCCl_3$ in chlorine content, when injected, would be excreted in an amount that would make any noticeable change in the urine. It was found that the chloride content was markedly increased indicating that the organism was capable of excreting the chlorides if they were formed.

To further test this theory, the effect of anesthesia, alone, then anesthesia followed by the injection of an amount of NaCl equivalent in chlorine content to the dosage of $HCCl_3$ and anesthesia followed by chloroform were studied, and it was found that anesthesia played no rôle in preventing the chlorides from being excreted if they were formed.

Lastly the inhibiting factor of alkali was studied to corroborate the previous findings and to determine, if possible, its therapeutic value. In our entire series of experiments only one rabbit lived for 48 hours, one lived thruout the experiment, and five died at the end of 24 hours. We agree with Davis and Whipple that alkali has no inhibiting action on $HCCl_3$ poisoning, nor does the presence of the alkali induce any change on the chloride output other than that effected by the diet.

Summary

1. The observations recorded fail to support the view that in chloroform poisoning the HCl formed is to be regarded as the toxic factor.

2. A diet yielding a basic ash has no inhibiting influence upon delayed chloroform poisoning.

3. The urinary changes of chloroform poisoning in starving animals do not vary markedly from the normal.

4. The only metabolic changes observed with the alkaline diet, that could not be explained by the food, were alterations in the creatinine, creatine and total nitrogen excretion. These are probably the results of absorption of dead tissue following $HCCl_3$ injury.

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THE INFLUENCE OF BENZYL BENZOATE UPON NITROGENOUS METABOLISM.

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Introduction

In recent years, benzyl benzoate has attained an immense popularity with the medical profession. Its widespread and almost universal usage in a multiplicity of clinical disorders has stimulated queries relative to the effects of this therapeutic agent upon metabolism. The pharmacodynamics of this and similar related organic esters has been thoroughly demonstrated by some of the ablest pharmacologists and the rational application of these facts has demonstrated that benzyl benzoate will be a valuable addition to the physician's armamentarium.

The metabolism of benzoic acid and sodium benzoate has been studied in detail by innumerable investigators. Sodium benzoate has been of especial toxicological interest, inasmuch as it has been used as a food preservative (concentration of 0.1 per cent.). Otherwise the benzoates have enjoyed little popular usage, except the employment of benzoic acid as an expectorant, and in the form of benzoin for chapped hands, etc.

Does benzyl benzoate participate in the apparent low toxicity of other benzoates? Has it any deleterious effect upon the maintenance and equilibrium of normal endogenous processes? By virtue of its double ring structure, has it a cumulative effect, as compared with the simple benzoates, or has it a chemical idiosyncracy of its own?

With these questions in mind, a study of the urinary metabolites under various experimental conditions has been carried through.

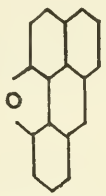
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* The data are taken from the thesis of Dr. George T. Pack presented in candidacy for the degree of Doctor of Medicine, Yale University, 1922.

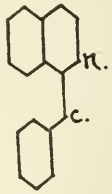
Historical.

The classical researches of Macht on the action of the opium alkaloids have emphasized the pharmacological importance of some of their derivatives[1]. He demonstrated that morphine and all its derivatives, except peronine or benzyl-morphine, stimulate the contractions of the ureteral rings and increase their tonicity, while all the the members of the papaverine group, namely papaverine, narcotine and narceine inhibit the contractions of the ureter and lower its tonus[2].

The morphine group possesses the pyridine phenanthrene skeleton, while the benzyl-isoquinoline grouping is peculiar to the papaverine molecule.



Pyridine-Phenanthrene Skeleton



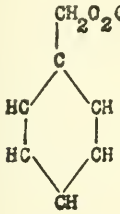
Benzyl-Isoquinoline Skeleton

By an ingenious pharmacodynamic analysis of the action of papaverine, he concluded that the selective inhibitory and tonus lowering properties of papaverine must reside in the benzyl radical of the benzyl-isoquinoline skeleton.[3]

The strength of this selective affinity of the benzyl radical is demonstrated by the fact that a small quantity of papaverine is sufficient to overcome the peripheral spastic effect of ten times the same dose of morphine.[4] This explains the anomolous effect of peronine or benzyl-morphine which, unlike all other morphine alkaloids, inhibits the contractions of the isolated ureters.

Macht then searched for simple non-alkaloidal and non-narcotic compounds containing the benzyl radical. He discovered two esters, benzyl benzoate and benzyl acetate.[5] The benzoate is preferably dispensed for therapeutic application for gastronomic reasons.

The physical properties, in brief, of benzyl benzoate are: liquid, but below 16°C. it solidifies in the form of leaflets; boiling point 323°C.; specific gravity at 15.5°C., 1.1210; insoluble in water but fairly soluble in strong alcohol and in olive oil; practically odorless.



Benzyl Benzoate ($C_{14}H_{12}O_2$)

Since this specific action of the benzyl grouping has been found to hold good also for other kinds of smooth muscle[6], its therapeutic application has been advised in the following clinical conditions.

(1) Excessive intestinal peristalsis, as in diarrheas and in dysentery[7].

(2) Intestinal colic and enterospasm (post-operative and other types).

(3) Pylorospasm.

(4) Spastic constipation.

(5) Biliary colic.

(6) Ureteral or renal colic.

(7) Spasm of urinary bladder.

(8) Uterine colic. (Spasmodic dysmenorrhea)[8].

(9) Circulatory conditions as angina pectoris[9], hypertension[10].

(10) Bronchial spasm or asthma[11].

(11) Whooping cough. [12] [13]

(12) Persistent hiccoughs.[14]

(13) Seasickness.[15]

The number of benzyl compounds is rapidly increasing. Benzyl alcohol has been recommended as an efficient local anaesthetic[16], its advantages being that it permits of sterilization by boiling and also possesses a certain antiseptic action.[17] It is interesting to note that benzyl alcohol has a depressive action

upon striated muscle, even when an animal is curarized, hence the action is upon the muscle fiber itself[18].

Volwiler and Vliet[19] have recently studied the rates of hydrolysis of various new benzyl esters. They state that it is essential to know whether the effects of the benzyl esters are due to the entire benzyl ester molecule or to benzyl alcohol formed by hydrolysis of the ester in the body. If it develops that the action is due to the benzyl alcohol split off in the body by hydrolysis of various new benzyl esters. They state that it is essential proportional to the rates of hydrolysis of the esters. On the other hand, if the effect is due to the intact benzyl ester molecule, the esters that are more slowly hydrolyzed in the body would probably have the more pronounced action. The rates of hydrolysis of a number of benzyl esters in dilute alcoholic KOH solution, increase in the following order: Salicylate, benzoate, stearate, cinnemate, acetate, succinate and fumerate. Nielsen and Higgins[20] have verified the fact that with these same benzyl esters, the power to relax smooth muscle and thereby relieve spasmodic pain is proportional to their rates of hydrolysis.

Probably the most widely employed of these new benzyl esters is benzyl succinate. Macht claims for it an equal toxicity with benzyl benzoate[21]. Bye[22] demonstrated the suprising fact that a guinea pig may take by mouth al least 10 grams of benzyl succinate per kilogram of body weight without harm and that rabbits may ingest at least 6 grams per kilogram of body weight and show no bad results. Comparative subcutaneous injections of the benzyl succinate and the benzyl benzoate show the former to be less toxic than the latter, and inasmuch us the benzyl group — which is recognized as the significant group — makes up a far greater proportion of the molecule of benzyl succinate (61.08 per cent versus 42.89 per cent of the benzyl benzoate) it would be inferred that perhaps the benzyl radical is not the toxic portion. Whether this comparative toxicity is applicable in the effects of these esters upon endogenous metabolism, will be determined later in the course of this investigation.

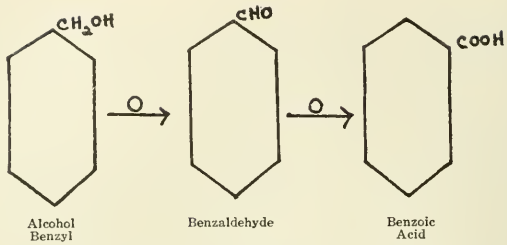
However, other experiments seem to point to the benzyl grouping as a poisonous radical, Macht and Fisher[23] demonstrating that papaverine was an efficient parasiticide for paramecia; and Macht and Weiner[24] showing that the benzyl

grouping of papaverine is the toxophoric portion which is responsible for its trypanosomacidal action (in vitro).

In rabbits the introduction of benzyl benzoate leads to destruction of leucocytes, as manifested by a leucopenia, the extent and rapidity of action being directly proportional to the dosage of the drug[25]. One cubic centimeter per kilogram of rabbit was the common dosage. In the presence of latent or quiescent infections in rabbits, larger doses produce an acute return of the disease. These results are almost indentically similar to the action of benzol. It is well known that benzol is leucotoxic (Selling), in fact it has been much employed for this purpose in leukemia. It likewise produces a leucopenia in rabbits (Weiskotten) and depresses the anti-infectious powers of the body (Rusk, Hektoen). It is questionable if the leucotoxic effect in itself, by virtue of the end-products of leucocytic decomposition, is quantitatively sufficient to produce a marked change in the urinary metabolites.

However, it is possible that the same toxic action towards paramecia, trypanosomes and leucocytes might also act upon the body cells as a general protoplasmic poison, since it has been demonstrated that the benzyl grouping has a direct depressing action upon various tissues. In variance with some of the above conclusions, Wiley states that benzoic acid and benzoates tend to produce a slight leucocytosis. Heller and Steinfield moreover state that benzyl benzoate has no toxic effect upon the leucocytes of the rabbit. The difference of opinion is probably due to the dosage employed, as normal amounts of the drug have no discernible toxic effects.

When these various benzyl esters and compounds are taken by mouth and also when introduced parenterally they are metabolized in the body with the liberation of the benzyl radical, which exerts its specific effect upon the tissues directly (muscles especially). Macht has observed that the benzyl compounds are excreted largely in the form of hippuric acid[16]. It has long been known that benzoates are excreted mainly as hippuric acid. The benzyl radical in all of the esters probably is converted to benzoic acid before hippuric acid is formed, as:



Now. $C_6H_5COOH + H_2N.CH_2COOH = C_6H_5CO.HN.CH_2COOH$

Benzoic Acid — Glycocoll — Hippuric Acid

All of the above mentioned historical facts tend to establish the hypothesis that the various benzyl compounds may have an influence upon normal metabolic behavior. Of course, in such a study, the elementary benzoic acid must be considered also in some detail.

Experimental

Methods.—Normal fasting dogs were employed throughout the course of the experiment. Female dogs only were used, due to the greater ease of catheterization. The animals were kept in the ordinary metabolism cages. Catheterization was practised every twenty-four hours, so that the total twenty-four hour specimen of urine consisted of the catheterized portion, bladder washings, bottle collection and cage washings. Sterile precautions were observed, none of the animals developing cystitis. Water was given ad libitum.

The volume, specific gravity, total acidity, pH etc., were determined in addition to some of the urinary metabolites. The methods used are as follows:

(1) *pH.*—This was determined on the catheterized specimens only. The Sorensen standards were employed in two experiments while in the remainder Clark and Lub's standards served instead[26].

(2) *Titratable Acidity.*—Folin's method[27].

(3) *Creatinine.*—Folin's colorimetric method[27].

(4) *Creatine.*—Folin-Benedict method[28]. The creatine is expressed as creatinine.

(5) *Total Phosphates* (P_2O_5).—Uranium acetate method.

(6) *Total Nitrogen.*—Kjeldahl method.

(7) *Reducing Test.*—These tests were not made, unfortunately until late in the course of the experimentation. The reducing substances were expressed quantitatively in terms of grams of glucose. Benedict's qualitative and quantitative methods were used[29].

The period of experimentation on each dog extended over six to ten days. As a rule, analyses were made on two to three twenty-four urine specimens before administering the drug, and then subsequent analyses for five to six days. Six different series of experiments were carried out as follows:

(1) The influence of fasting upon urinary composition. These controls were done on dogs, which were also used in other experiments to demonstrate the action of the drug.

(2) The influence of a small dose of benzyl benzoate upon urinary composition. (½ c. c. per kg. of body weight). The pure benzyl benzoate was given by stomach tube.

(3) The influence of a moderate dose of benzyl benzoate upon urinary composition. (1 c. c. per kg. of body weight.) The method of administration was the same as in 2.

(4) The influence of a large dose of benzyl benzoate upon urinary composition. (2 c. c. per kg. of body weight.) Same method of administration.

(5) The influence of benzyl succinate upon urinary composition. (1 gm. per kg. of body weight.) This drug was placed in gelatin capsules and orally administered.

(6) The influence of sodium benzoate upon urinary composition. Considerable difficulty in administration was experienced owing to gastric irritation leading to vomiting. Eventually, however, success was attained in certain animals.

The Influence of Fasting upon Urinary Composition.

In order to determine the specific effect of benzyl benzoate upon nitrogenous metabolism, it is necessary to establish a base line of the normal metabolism in dogs, fasting over a period of time equal to that of the benzyl benzoate experiment.

These dogs, Tables I and II and Plate I, before fasting were healthy, well-nourished animals. Dog 1 was considerably fatter than dog 2. The loss in weight during the eight days of

starvation was gradual and constant in both animals. The titratable acidity and pH of the urine maintained a parallel and constant strength with little variation, throughout the course of the control experiment. The duration of the period of fasting was too short to cause any noticeable manifestations in the urine of starvation acidosis. Howe and Hawk[30], however, note an increased total acidity during a ten day fasting period of a human being.

TABLE I.

The Influence of Fasting upon Urinary Composition.

Dog 1. Hound. Weight 15 kg. Starvation began April 10, 1922.

Date	Weight	Volume	Specific Gravity	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.				mgms.	mgms.	mgms.	gms.	gms.	
April 12		225		5.8	205	532.8	430.8	102.0	0.49	2.67	5.44
" 13	14.3	140	1.030	5.8	184	532.8	405.0	127.0	0.40	2.61	6.52
" 14		120	1.035	6.0	205	540.0	413.2	126.7	0.44	2.67	6.06
" 15	13.8	115	1.040	5.8	188	540.0	405.0	135.0	0.47	2.52	5.36
" 16		110	1.042	6.0	210	506.2	405.0	101.2	0.57	2.34	4.10
" 17	13.5	110	1.040	6.0	197	519.2	405.0	114.2	0.53	2.50	4.71
" 18		110	1.037	6.1	184	613.6	421.8	191.7	0.39	3.03	7.76

Remarks — Daily reduction and acetone tests were negative.

TABLE II.

The Influence of Fasting upon Urinary Composition.

Dog 2. English bull. Weight 13.3 kg. Starvation began April 12, 1922.

Date	Weight	Volume	Specific Gravity	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.				mgms.	mgms.	mgms.	gms.	gms.	
April 14		190	1.032	7.0	111	460.2	349.1	111.0	0.66	3.30	5.0
" 15	12.6	200	1.041	7.0	128	523.1	321.5	201.6	0.58	2.52	4.3
" 16		75	1.050	6.8	132	578.5	321.4	257.0	0.62	2.25	3.6
" 17	12.0	95	1.040	6.8	145	493.9	310.0	183.9	0.48	2.34	4.8
" 18		90	1.040	6.2	145	578.5	277.1	301.3	0.49	2.73	5.5
" 19	12.0	90	1.043	6.6	158	531.5	324.6	206.8	0.46	2.45	5.3
" 20		70	1.045	6.4	150	506.2	281.2	225.0	0.40	2.55	6.2

Remarks — Daily reduction tests were negative.

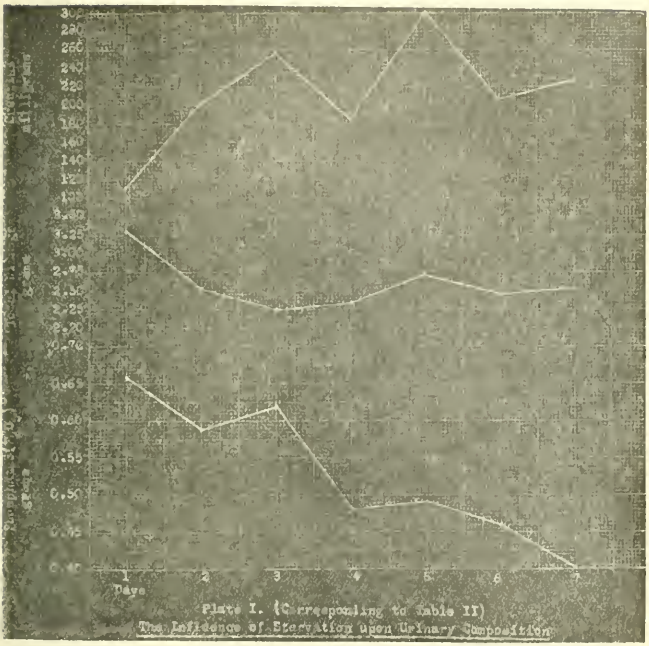


Plate I. (Corresponding to Table II)
The Influence of Starvation upon Urinary Composition

Total nitrogen excretion remained constant. Lusk states that in prolonged fasting the nitrogen output sinks much below the figures of the earlier days. Here again the short period of starvation is responsible for this seeming contradiction. In a series of previous experiments Underhill[31] noted that on the second day of fasting there was a drop in total nitrogen excretion of dogs, but for the succeeding ten days there was no apparent change in the nitrogen output. The work of Howe and Hawk[30] likewise confirms this finding.

The total phosphates of the urine gradually decreased in one animal (see Plate I) while in the other (Table I) there was considerable variation before the final drop. Lusk maintains that during starvation there is a greater phosphoric acid excretion, which Munk attributes to osseous catabolism. The find-

ings in the present experiment corroborate those of Hawk[32], who observed a decrease of three hundred per cent in the phosphate excretion in a fasting period of equal duration.

Hence in this short starvation experiment the N/P_2O_5 ratio must necessarily increase if the phosphate excretion diminishes while the total nitrogen remains a constant. E. and O. Freund observed that the N/P_2O_5 ratio decreased markedly in the professional faster Succi.

The creatinine elimination in both animals was not modified by the fast, there being little quantitative variation from day to day. Mendel and Rose[33] have likewise found this to be the case. Folin, van Hoogenhuyze and Verploegh, Klercker, Closson and Shaffer have shown that the daily output of creatinine on a meat free diet is remarkably constant for the same individual, being, moreover, independent of the total nitrogen and the volume of the urine. Mendel concludes that the constancy of creatinine excretion indicates that it is of endogenous origin, while Folin says, "it is an index of a certain kind of protein metabolism occurring daily in any given individual".

Under normal conditions the creatine elimination in adult dogs is very slight. It has long been known that during starvation there is a marked increase in the creatine of the urine. Our control animals proved no exception in this instance. This appearance of creatine had been attributed to the elimination of creatine liberated thru muscle breakdown; but has now been explained as due to lack of carbohydrate metabolism[34]. That an increased protein catabolism is not the principal agent in the production of creatinuria during fasting, may be assumed, if we note that the total nitrogen and phosphate excretion are not increased at the same time. Furthermore only twelve to eighteen per cent of the body energy during fasting is derived from the tissue protein, the remainder being contributed by the fats (Lusk). The question of creatine elimination will be considered in more detail later.

Only the relative curves of the excretion of these metabolites may be accepted in these dogs. The exact quantitative data would not be applicable for comparison in other series of this experiment where they are used, as it is well known that "a repeated fast is accompanied by less protein loss from the body than the original fast" (Howe and Hawk[30]).

The Influence of Benzyl Benzoate upon Urinary Composition — Small Dose.

The administration of benzyl benzoate is not followed by any noticeable toxic symptoms. Indeed, the drug appears to be sedative, as animals previously lively, become drowsy and lethargic.

The data in Tables III and IV and Plate II show that the weight loss is not accelerated and that the volume of urine is not increased beyond that caused by the greater fluid intake. In this respect benzyl benzoate does not differ from other benzoates as Sollmann observed that diuresis does not occur. This holds if the benzoates are entirely converted to hippuric acid, but if larger doses are ingested then benzoic acid may be excreted as such, in which case diuresis is a possibility.

TABLE III.

The Influence of Benzyl Benzoate upon Urinary Composition — Small Dose.

Dog 3. Black spaniel. Weight 8.4 kg. Starvation began March 25, 1922.

Date	Weight	Volume	pH Brom Cresol Purple	Titratable acidity, cc of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio	Reduction test
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.		gms.
March 29	8.0	200	6.0	174	305.8	183.0	122.8	0.49	1.51	3.0	0
" 30				Urine specimen lost.							
" 31	7.7	200	6.0	120	304.5	208.7	95.7	0.41	1.83	4.4	0
April 1		550	5.8	128	430.0	186.9	243.1	0.40	2.19	4.4	3.4
" 2		160	5.6	149	788.8	192.0	596.7	0.45	2.39	5.3	1.4
" 3	7.4	80	5.8	77	462.2	177.7	284.4	0.30	1.98	6.6	0
" 4		75	6.0	91	510.6	188.0	322.6	0.29	1.93	6.6	0
" 5	7.2	70	6.0	145	413.2	200.4	212.7	0.26	1.98	7.6	0

Remarks — April 1: 3.9 cc. of Pure Benzyl Benzoate given per os. ½ cc. per kg. of body weight.
The positive reduction tests were due to glycuronates, which were quantitatively expressed in terms of grams of glucose.

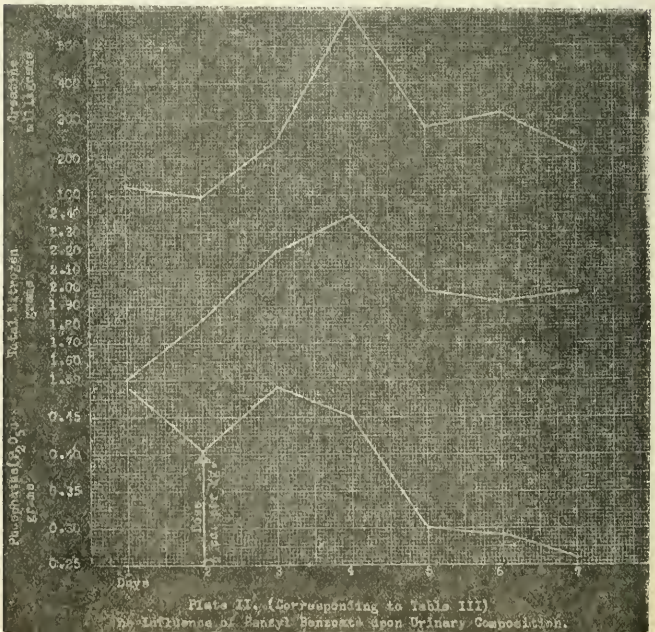
TABLE IV.

The Influence of Benzyl Benzoate upon Urinary Composition — Small Dose.

Dog 4. Bull terrier. Weight 10 kg. Starvation began March 25, 1922.

Date	Weight	Volume	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.	
March 29	10.0	750	6.4	153	634.9	395.0	239.9	0.63	4.74	7.5
" 30					Urine contaminated by feces.					
" 31	9.5	450	6.2	137	318.9	208.7	110.1	0.39	2.79	7.1
April 1		300	6.1	128	285.8	184.0	101.7	0.37	2.91	7.8
" 2		200	6.0	93	490.9	190.9	300.0	0.31	2.42	7.8
" 3	9.2	315	6.0	108	458.2	179.7	278.4	0.30	2.25	7.5
" 4		355	6.2	109	465.1	188.0	277.1	0.33	2.24	6.7
" 5	9.0	350	6.2	205	450.0	180.8	269.2	0.27	2.13	7.8

Remarks — April 1: 5 cc. of pure Benzyl Benzoate given per os. ½ cc. per kg. of body weight.
Daily acetone and reduction tests were negative.



In both controls the titratable acidity of the urine and pH were not modified by the amount given. One would not expect a marked increase, since the hippuric acid formed is a weak acid and does not dissociate with ease. Blatherwick notes, however, a gradual increase in titratable acidity and H ion concentration of the urine in a human, ingesting three grams of benzoic acid per day.

The total nitrogen and phosphate output are variable with this small dosage. In one instance the nitrogen and phosphate are slightly increased (Table III), while in Table IV the phosphate excretion diminishes unmodified, the nitrogen rise being insignificant. McCollum and Hoagland[35] have similarly observed that when the quantity of benzoic acid ingested is not excessive, there is no noticeable rise in the total nitrogen excreted. The variability in these constituents together with other variations mentioned later, tend to establish the hypothesis that the given dosage was on the border line between a maximal average and a toxic dose, as far as tissue catabolism is concerned.

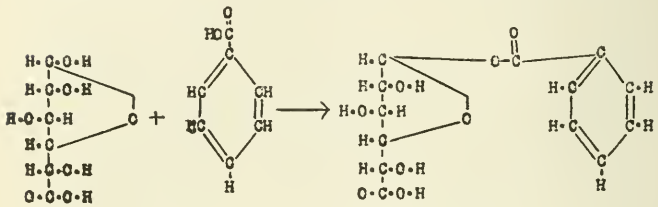
The daily creatinine content of the urine was not affected by this dosage of benzyl benzoate. This confirms the findings of Lewis and Karr in 1916, with other benzoates. The most remarkable change was in the creatinuria induced. This very marked increase occurred mainly as late as the second day after ingestion of the drug, and then gradually fell.

In one instance (Table III) reduction tests were positive after the administration of the drug. Conjugate glycuronates were responsible for this as determined by qualitative analyses. The glycuronates are non-fermentable and are levorotary. (Care must be taken in clearing the urine before spectroscopy with lead acetate as this chemical precipitates the glycuronates).

After hydrolysis, reduction still occurs but the plane of polarized light rotates to the right as glycuronic acid is dextrorotary. The amount of reduction was measured and the total quantity expressed as glycuronates in terms of grams of glucose. The presence of reducing substances in one instance (Table III) and their absence in Table IV coincide with the previous observations on total nitrogen relative to the variable effects of such a dose of benzyl benzoate.

The appearance of glycuronates in the urine is not peculiar

to benzyl benzoate. It has long been known that benzol derivatives cause the appearance of glycuronic acid (in conjugation) in the urine. Dakin in 1910 gave men 5-10 grams of sodium benzoate in 5 per cent solution, daily for 3 days, and observed in consequence an increase in the glycuronic acid content of urine, which reduced Fehling's solution[36]. Lewinski also noted this phenomenon. The glycuronic acid is never excreted free, but always in combination with other substances.



This combination is an ester type of union as portrayed above by Sherwin[37]. The origin of glycuronic acid is at present not known. It is a question as to whether it is formed from glucose or whether it originates entirely independent of glucose metabolism. Sherwin[37] cleverly explains the glucose origin as follows: "It is unreasonable to suppose that this carbohydrate-like compound should be directly synthesized by the body when it could be obtained as simply from glucose. On the other hand, it seems highly improbable that it is a normal catabolic product of glucose since the aldehyde group, which would certainly be the first point of attack when the glucose molecule is subjected to oxidation, is still present in the glycuronic acid. Furthermore, the fact that after ingestion of large amounts of glycuronic acid we find gluconic acid, saccharic acid and much oxalic acid in the urine means simply this, that glycuronic acid is oxidized with difficulty, but does not indicate that it is a normal intermediary product of glucose catabolism. The most plausible explanation of the origin of glycuronic acid is; a union is effected between the aldehyde group of glucose and the foreign molecule, by which the former is protected against further oxidation. The next point

of attack then is the primary alcohol group which is converted accordingly into a carboxyl".

Mandel and Jackson[38] in 1902 conducted an interesting experiment on glycuronate origin and elimination. They administered camphor to fasting dogs for several days and noted the appearance of glycuronic acid in the urine. The giving of large quantities of glucose caused a drop in the protein metabolism together with a decrease in the elimination of glycuronic acid. Upon giving the animal chopped meat the quantity of campho-glycuronic acid in the urine was correspondingly increased. Lusk infers from the above that glycuronic acid is produced solely in the intermediary metabolism of protein.

It is interesting to note that all of the benzoate plus the benzoic acid derived from the benzyl radical is not excreted in combination with glycocoll, but some of it is conjugated with glycuronic acid. Indeed, the calling forth of glycuronic acid to combine with benzoic acid may be due to the lack of sufficient glycocoll to supply the demand. The creatinuria together with the hippuric acid formation occurring simultaneously makes worthy of consideration the view that protein is also the mother substance of the glycuronic acid.

The Influence of Benzyl Benzoate upon Urinary Composition—Moderate Dose

If a dosage, as large as that given in the preceding series, creates such little change in the chemical behavior of the body cells, a slightly smaller dose would give insignificant or negative results, as far as our methods of determination are concerned. Consequently the dosage was increased to one cubic centimeter per kilogram of body weight, in order to magnify these changes, toxic or otherwise, and also to see if our former variable results would assume a consistency. (See Tables V, VI, VII and Plate III.

The loss of weight and volume output of urine are not modified in the least. Altho the H ion concentration is only slightly increased in two instances (Table V and VI), the titratable acidity is elevated considerably in each dog, by the administration of this drug. In two of the three dogs the increased acidity occurred on the day after ingestion, in the

other on the second day. In every case the increased acidity was only temporary, usually continuing for forty-eight hours.

It is a noticeable fact that the greatest increase in phosphates and in titratable acidity are simultaneous in appearance, and their subsequent diminution in output concurrent. Probably the acid phosphates are responsible for the increased acidity.

TABLE V.

The Influence of Benzyl Benzoate upon Urinary Composition — Moderate Dose

Dog 1. Hound. (Same dog as in Table I.) Weight 15 kg. Starvation began March 4, 1922.

Date	Weight	Volume	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.	
March 9		110	6.0	150	437.8	395.1	42.7	0.55	2.82	5.1
" 10		100	5.8	139	537.2	413.2	124.0	0.57	2.91	5.1
" 11	14.0	120	5.8	125	506.2	415.3	90.8	0.46	2.96	6.4
" 12		160	5.8	220	1002.5	405.0	597.5	0.97	4.35	4.5
" 13	13.8	180	5.8	192	810.0	440.2	369.8	0.62	5.25	8.4
" 14		140	5.8	150	675.0	405.0	270.0	0.44	4.26	9.7
" 15	13.5	135	5.6	163	653.2	389.4	263.7	0.43	3.63	8.4
" 16		120	5.6	133	482.1	352.1	129.8	0.32	3.32	10.3

Remarks — March 12: 14 cc. of Pure Benzyl Benzoate given per os. 1 cc. per kg. of body weight.
Reducing tests were not done until March 15 and 16, when positive tests were obtained.

TABLE VI.

The Influence of Benzyl Benzoate upon Urinary Composition — Moderate Dose.

Dog 2. English bull. (Same dog as in Table II.) Weight 15.4 kg. Starvation began March 4, 1922.

Date	Weight	Volume	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.	
March 9		225	6.0	172	506.2	385.7	120.5	0.64	2.93	4.5
" 10		190	6.2	182	562.5	413.2	149.2	0.67	3.00	4.4
" 11	14.4	200	6.2	146	578.5	418.9	159.6	0.57	3.06	5.3
" 12		160	5.8	184	1002.5	326.6	675.8	0.75	3.30	4.4
" 13	13.9		Urine lost							
" 14		220	6.0	165	809.9	545.1	264.7	0.72	2.60	3.6
" 15	13.8	140	5.8	165	450.0	316.4	133.5	0.40	2.67	6.6
" 16		140	5.8	94	349.1	321.4	27.7	0.37	2.80	7.5

Remarks — March 12: 14.4 cc. of Pure Benzyl Benzoate given per os. 1 cc. per kg. of body weight.
Reducing tests were not done until March 15 when a positive test was obtained.

TABLE VII.

The Influence of Benzyl Benzoate upon Urinary Composition — Moderate Dose.

Dog 5. Mongrel. Weight 9.8 kg. Starvation began March 8, 1922.

Date	Weight	Volume	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio	Reduction test
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.		gms.
March 12		130	5.6	216	324.0	253.1	70.8	0.83	3.99	4.8	0
" 13	9.2	?	5.4	185	342.2	304.1	38.1	0.81	4.05	5.0	0
" 14		110	5.4	154	281.2	213.1	68.1	0.57	3.40	5.9	0
" 15	8.8	100	5.4	145	578.5	238.2	340.2	0.70	3.72	5.3	3.8
" 16		200	5.4	295	694.2	202.5	491.7	1.36	5.47	4.0	6.8
" 17		150	5.4	197	777.5	255.7	521.8	0.26	4.20	16.1	7.1

Remarks — March 15: 9.2 cc. of Pure Benzyl Benzoate given per os. 1 cc. per kg. of body weight.

Subsequent analyses were prevented by contamination of the urine on two successive days.

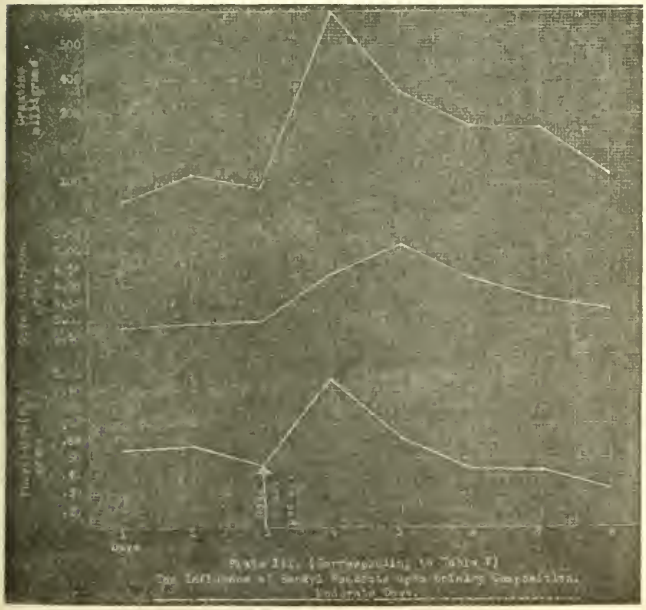


Plate III. (Corresponding to Table V)
The Influence of Benzyl Benzoate upon Urinary Compositions.
Moderate Dose.

Not only the phosphate but the total nitrogen excretion also is considerably elevated. The increase is variable in amount and time of appearance after administration of the drug. Altho it may drop immediately after ingestion, the N/P_2O_5 ratio then gradually increases as the time advances. This is due to the fact that the augmentation of nitrogen excretion persists longer and when diminution does occur it never decreases proportionately, as quickly as do the phosphates.

Glycuronic acid excretion was present with each dog and in one instance (Table V) persisted as late as the fifth day after administration. Unfortunately reduction tests were not employed throughout these experiments.

The marked creatinuria was again noted, this being accompanied by no change in the creatinine output. Is this enormous creatine output (400—600 per cent increase) due directly to the action of the drug in causing a breakdown of body protein or is it the indirect result of an interference with the mechanism that regulates creatine utilization? There are many minor causes of creatinuria. An excessive water intake is accompanied by the appearance of some creatine in the urine, possibly due to a flushing out of the tissues, but a polydipsia has not been concomitant in all cases with the administration of benzyl benzoate. Acidosis may be accompanied by a creatinuria[39]; but the association is not always causal, but both may find origin in some other disturbance, as for instance, the lack of or inability of the organism to utilize carbohydrate. Moreover creatinuria may be present during carbohydrate deficiency even in the absence of acidosis. Repeated tests for diacetic acid were negative. These with the diminutive increase in the H ion concentration easily contradict the acidosis hypothesis.

Mendel and Rose[33] have made the statement that total nitrogen and total creatinine appear to have a common source, for an increase or decrease in the latter is always accompanied by a similar change in the former. This is directly contradictory to Benedict and Osterberg[34] whose experiment must be cited. They used phlorhizinized dogs because of the relative inability to utilize carbohydrate; moreover there being a relatively enormous elimination of nitrogen and of creatine from the tissues. In their own words: "If the creatine of the urine has its origin in the destruction of muscular tissue

as has been assumed, a sparing of the body tissue destroyed by feeding exogenous creatine-free protein should have caused a corresponding fall in the creatine eliminated, but if the utilization (or destruction) of creatine be dependent upon carbohydrate utilization, the ingestion of exogenous protein in the phlorhizinized dog should not appreciably affect the output of creatine in the urine, which was the case in this experiment". According to this reasoning there is no parallelism between body tissue destroyed and creatine elimination, as the latter is totally unaffected whether the nitrogen of the urine represents body tissue catabolized or whether it is derived from exogenous creatine-free proteins. This does not prohibit the possibility that the creatine may originate from the exogenous protein administered even if washed creatine free. Denis produced creatinuria in women by a heavy protein ingestion. Steenbock and Gross[40] produced a creatinuria in pigs by feeding either casein or edestin. Rose, Dimmitt and Cheatham[41] on the other hand, claim that protein feeding (egg albumin) in starving man reduces the creatine output to nil. Such contradictory data do not clarify the question.

Could a sudden inhibition of the carbohydrate utilizing function of the body be responsible for all of these urinary changes? Does the benzoic acid or the benzyl radical prevent carbohydrate utilization?

It is universally known that glycocoll may be either completely or partially transformed to dextrose. The stages through which this occurs have been outlined by Lusk. In the first place it is assumed that the initial change is a hydrolytic deamination whereby ammonia is formed and a hydroxy group is added to the denitrogenized amino acid. According to this view glycocoll would first be changed to glycolic acid, which on reduction would yield glycolic aldehyde, three molecules of which will form one molecule of glucose.

(See Underhill — Physiology of Amino Acids, pg. 111).

$$3\ \begin{matrix}CH_2.NH_2\\ |\\ COOH\\ \text{Glycocoll}\end{matrix} + H_2O = 3\ \begin{matrix}CH_2.OH\\ |\\ COOH\\ \text{Glycolic Acid}\end{matrix} - 3O = 3\ \begin{matrix}CH_2.OH\\ |\\ CHO\\ \text{Glycolic Aldehyde}\end{matrix} = C_6H_{12}O_6\ \text{Dextrose}$$

Any mechanism which causes a marked elimination of glycocoll from the body causes a profound disturbance of the sugar metabolism[42]. Benzoic acid by virtue of its hippuric acid formation might produce such a disturbance. Let us surmise that the demand of benzoic acid for conjugation with glycocoll is very acute, glycocoll synthesis might be unable to cope with the situation so that there is a breakdown of body protein to supply a part of this emergency requirement[43 44]. We could imagine that glycocoll is removed from the large protein molecule, which as a result may disintegrate at least in part; and the products of disintegration may not be those of normal complete proteolysis, but such bodies as creatine. Umber[45], for instance, states that the glycocoll is abstracted from the globulin molecule of the tissues, but this is denied by Abderhalden[46].

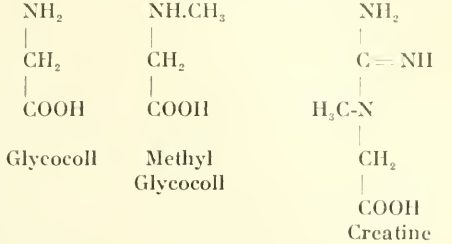
Returning to the situation where there is a lack of glycocoll, it might be considered that the part which glycocoll plays in the metabolism or formation of sugar, might be undertaken by some other amino acid, arginine, for instance. Arginine may serve as a source of glucose, in which case it is probable that the sugar comes from the ornithine moiety with five carbon atoms, into which it may be converted by the action of arginase. Such an abnormal demand upon the conversion of arginine into glucose might be accompanied by anomalous products from arginine. Instead of attempting to shoulder this work left by the departed glycocoll, arginine by transformation or cleavage may give rise to glycocoll itself. Arginine may be one source of creatine by catabolism into guanidine, as it has been demostrated by Lewis and Karr[47] that products of metabolism which might otherwise go to the formation of urea, may be diverted to the production of glycocoll.

Thompson[48] observed an increase in creatine excretion and the muscle content in creatine following arginine injection into dogs. Myers and Fine[49] obtained a higher muscle content in creatine for rats fed on the arginine-rich protein edestin. Inouye[50] observed some formation of creatine from arginine added to liver extracts, while Gross and Steenbock report that arginine given to pigs caused an increased creatine excretion.

Gross and Steenbock[51], moreover, suggest that the creatinuria which they produced in pigs by feeding thyroid gland might

be due to the acceleration of the oxidative system of arginine destruction at the expense of the effect of the arginase.

One of the older theories of the origin of creatine is that it is formed from the methylated glycocoll, combined with the guanidine residue, or modified urea rest[52].



It is very unlikely that such a process of formation occurs in the creatinuria induced by benzoates, because there is probably not enough glycocoll present to satisfy the benzoic acid, and even less to bring about creatine genesis.

The Influence of Benzyl Benzoate upon Urinary Composition—Large Dose

A dosage of 2 c.c. per kilogram of body weight does not appreciably change the excretory picture from that seen with half the dosage. (See Table VIII and Plate IV.) No new or different ratios or modifications are seen. The total nitrogen, phosphates and titratable acidity show their accustomed rise together with the creatinuria and glycuronuria.

The Influence of Benzyl Succinate upon Urinary Composition

The dosage of one gram of benzyl succinate per kilogram of body weight is not exactly equivalent in weight to one cubic centimeter of benzyl benzoate as the specific gravity of the latter is 1.1210. Even if equal parts by weight of these two drugs are used, the benzyl coefficient is not equal in the two cases since the succinate per unit weight contains more benzyl in combination[22]. If the quantitative metabolic disturbances are proportional to the amount of benzyl, the benzyl succinate

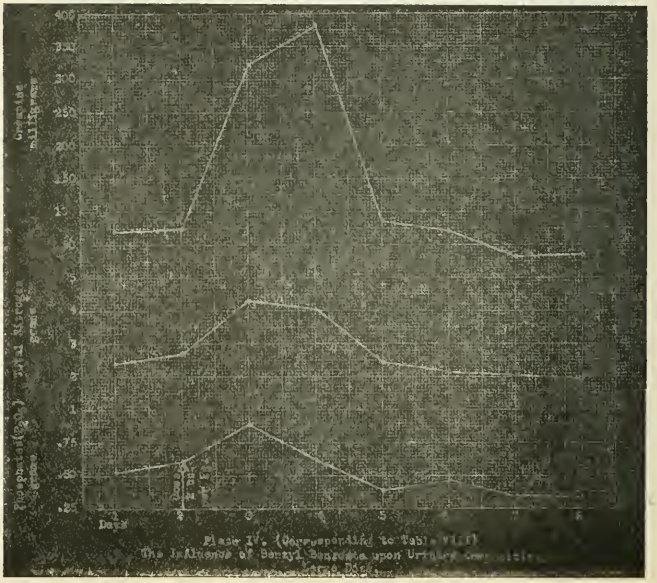
TABLE VIII.

The Influence of Benzyl Benzoate upon Urinary Composition — Large Dose.

Dog 5. (Same dog as in Table VII.) Weight 8.3 kg. Starvation began April 10, 1922.

Date		Weight	Volume	Specific Gravity	pH Brom Cresol Purple	Titratable acidity, cc of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio	Reduction Costa
1922		kg.	cc.				mgms.	mgms.	mgms.	gms.	gms.		
April	12		125		5.6	205	271.8	202.5	69.3	0.52	2.40	4.6	0
"	13	7.8	80	1.045	5.8	208	281.2	206.6	74.6	0.61	2.70	4.4	0
"	14		200	1.042	5.8	317	506.2	184.0	322.1	0.88	4.29	4.8	6.2
"	15	7.2	90	1.070	5.8	205	562.5	180.7	381.7	0.62	4.05	6.5	5.5
"	16		90	1.043	6.0	210	268.2	187.5	80.7	0.38	2.40	6.3	0
"	17	7.0	60	1.042	6.0	205	250.0	179.2	70.8	0.45	2.16	4.8	0
"	18		50	1.043	6.0	174	223.9	191.3	32.5	0.34	2.05	6.0	0
"	19	6.7	130	1.025		171	220.1	184.0	36.0	0.33	1.95	5.9	0

Remarks — April 12: 15.6 cc. of Pure Benzyl Benzoate given per os. 2 cc. per kg. of body weight.



weight for weight would no doubt produce the more marked change. However if these peculiar phenomena owe their origin to benzoic acid, directly or indirectly, we can readily assume that benzyl benzoate must be the more toxic of the two.

The pharmacological action of benzyl succinate manifests itself more slowly than benzyl benzoate, but this is due to the fact that the benzyl radical is not so quickly converted into benzyl alcohol in the tissues[21 19].

The combination of succinic acid with benzyl to form a relatively non-toxic ester is logical, since the introduction of carboxyl into the aromatic series lessens the toxicity of the benzyl group. The succinic acid itself introduced will have no toxic action, since it is one of the more abundant, non-nitrogenous extractives of muscle; dog muscle containing 0.16 gram per kilogram.

The benzyl succinate as used in therapy is a mono-benzyl form. It is suggested that two benzyl radicals be attached to the succinic acid forming a di-benzyl succinate. It would be interesting to know what advantages or disadvantages such a compound would possess.

$COOCH_2 - C_6H_5$	$COOCH_2 - C_6H_5$
CH_2	CH_2
CH_2	CH_2
$COOH$	$COOCH_2 - C_6H_5$
Mono-benzyl succinate	Di-benzyl succinate

From the data presented in Tables IX and X and Plate V it may be seen that the H ion concentration remains the same, as does the titratable acidity, except for some slight insignificant variations. Total nitrogen is increased almost as much as with benzyl benzoate, especially in Table X, whereas the phosphates and the creatine excretion have not responded to such an extent as with the benzoate. The creatine behavior is worthy of note, in one instance the maximum excretion occurring on the second day after exhibition of the drug, in the other on the first day. The urine of both animals contained no

creatine on the third day, after which there was a gradual daily increase similar to the creatinuria of fasting (see Plate V). Creatinine as usual remains undisturbed.

The conclusion derived from the above responses to benzyl succinate, is that metabolically speaking, the succinate is much less active than the benzoate of benzyl.

TABLE IX.

The Influence of Benzyl Succinate upon Urinary Composition.

Dog 6. Fox terrier. Weight 9 kg. Starvation began January 9, 1922.

Date	Weight	Volume	pH	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.	
Jan. 12		300	5.9R.	201	204.5	202.5	2.0	0.35	1.92	5.4
" 13		100	5.9R.	154	253.1	253.1	0	0.31	2.19	7.0
" 14	8.4	100	5.8R.	184	213.1	207.6	5.4	0.39	1.83	4.7
" 15		100	5.9R.	192	285.2	222.5	62.6	0.56	2.79	4.9
" 16	8.2	125	5.8R.	205	352.1	202.5	149.6	0.21	2.19	10.4
" 17		75	5.9R.	205	276.9	259.6	0	0.32	1.74	5.4
" 18	8.0	200	5.8R.	154	238.2	225.0	13.2	0.31	1.71	5.5
" 19		150	5.7M.R.	111	253.1	192.8	60.2	0.25	1.62	6.4

Remarks — January 15: 8.4 gms. of Benzyl Succinate given per os. in gelatin capsules. 1 gm. per kg. of body weight.
Nitrogen intake in the Gelatin capsules was 0.23 gms.
pH; M.R. = Methyl Red.
R. = Rosolic Acid.

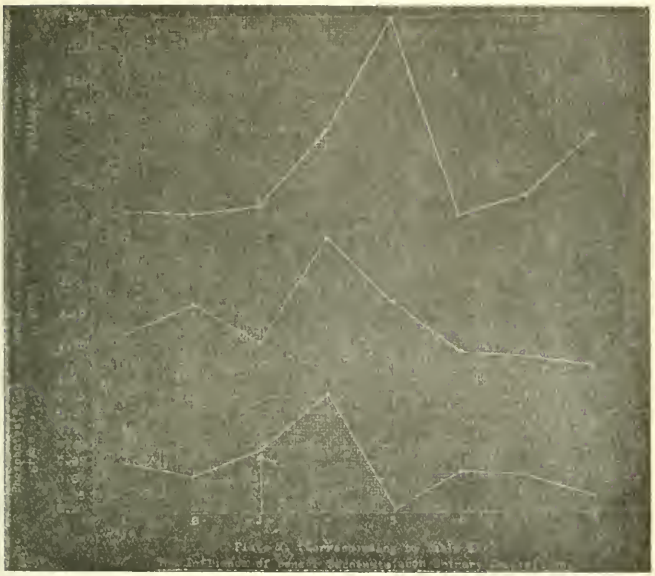
TABLE X.

The Influence of Benzyl Succinate upon Urinary Composition.

Dog 3. Black spaniel. (Same dog as in Table III.) Weight 7.7 kg. Starvation began January 11, 1922.

Date	Weight	Volume	pH	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio
1922	kg.	cc.			mgms.	mgms.	mgms.	gms.	gms.	
Jan. 13		125	5.7M.R.	231	237.5	206.6	30.8	0.59	2.70	4.5
" 14	7.4	125	6.2R.	282	207.6	184.0	23.6	0.62	2.22	3.5
" 15		125	5.9R.	222	368.1	176.0	192.0	0.81	3.84	4.7
" 16	7.0	150	5.8R.	175	295.6	179.2	116.4	0.53	2.79	5.2
" 17		60	5.9R.	189	210.3	192.8	0	0.57	2.13	3.7
" 18	6.7	80	5.8R.	188	184.0	176.0	7.9	0.44	2.19	4.9
" 19		60	5.9R.	188	206.6	168.7	37.8	0.43	2.04	4.7

Remarks — January 15: 7.4 gms. of Benzyl Succinate given per os. in Gelatin capsules. 1 gm. per kg. of body weight.
Nitrogen intake in the Gelatin capsules was 0.18 gms.
pH; M.R. = methyl red.
R. = rosolic acid.



THE INFLUENCE OF SODIUM BENZOATE UPON URINARY COMPOSITION

From the results of the former experiments one might suspect that the resultant changes are not necessarily due to the benzyl radical as such, but to the benzoic acid, whether present as benzoates or converted from the benzyl grouping.

Chittenden, Long and Herter[53] administered sodium benzoate dissolved in food or drink, 0.3 gram per day for two months, then 0.6 to 1 gram for one to two weeks. Throughout this experiment the composition of the feces, the nitrogen balance, the quantitative composition of the urine, and the distribution of nitrogen, remained within normal limits. Wiley[54] however states that with daily doses of 1 to 2.5 grams of sodium benzoate, given in capsules, there were both subjective and objective symptoms, including metabolic disturbances.

The experiments with sodium benzoate detailed in Tables

XI and XII and Plate VI show that in two days after administration of the drug, the individual loss of weight was approximately a kilogram. This reduction of body weight confirms Wiley's observation, it being more rapid than the controls.

The H ion concentration in dog 7 (Table XI) increased as usual, but in the other animal a diminution occurred. The titratable acidity together with the total phosphates were augmented by the drug.

The total nitrogen increase was even more marked than with benzyl benzoate. This is interesting if we note that the dose per kilogram contained only relatively the same amount of benzoate as was given with the dosage of 1 c. c. of benzyl benzoate per kilogram of body weight; the benzyl benzoate being potentially richer in benzoic acid because of the unconverted benzyl group.

TABLE XI.

The Influence of Sodium Benzoate upon Urinary Composition.

Dog 7. Boston Bull. Weight 10 kg. Starvation began April 10, 1922.

Date	Weight	Volume	Specific Gravity	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio	Reduction test
1922	kg.	cc.				mgms.	mgms.	mgms.	gms.	gms.		gms.
April 12		150		7.0	145	321.4	253.1	68.2	0.35	1.20	3.4	0
" 13	9.5				149	333.5	253.1	80.4	0.33	0.96	2.9	0
" 14			1.017	7.4	329	837.9	243.0	594.9	1.26	5.11	4.0	10.5
" 15	8.6	Urine lost during a convulsion										2.6
" 16		100	1.048	6.4	202	578.5	202.5	376.0	0.51	3.90	7.7	
" 17	8.3	100	1.041	6.4	188	506.2	202.5	303.7	0.51	3.06	6.0	0
" 18		90	1.056	6.4	162	337.5	198.5	138.9	0.45	2.49	5.5	0
" 19	8.1	110	1.044	6.4	162	324.0	184.0	139.9	0.34	2.37	7.0	0

Remarks — April 14: 7.25 gms. Na Benzoate given in Agar Agar by stomach tube. 0.76 gms. per kg. of body weight.
—April 15: Numerous convulsions.
0.764 gms. of Na benzoate per kg. of body weight contains relatively the same amount of benzoate as was given with the dosage of 1 cc. of Benzyl benzoate per kg. of body weight.

TABLE XII.

The Influence of Sodium Benzoate upon Urinary Composition.

Dog 3. Black spaniel. (Same dog as in Table III and X.) Weight 8.5 kg. Starvation began May 1, 1922

Date	Weight	Volume	Specific Gravity	pH Brom Cresol Purple	Titratable acidity, cc. of N/10 NaOH	Total Creatinine	Creatinine	Creatine as Creatinine	Phosphates (P_2O_5)	Total Nitrogen	N/P_2O_5 Ratio	Reduction test
1922	kg.	cc.				mgms.	mgms.	mgms.	gms.	gms.		gms.
May 4		110	1.037	5.8	246	313.9	232.7	81.2	0.44	2.52	5.6	0
" 5	8.2	110	1.035	5.8	222	263.0	210.9	52.0	0.45	2.09	4.5	0
" 6		800	1.023	5.8	354	764.1	180.8	583.3	1.24	4.74	3.8	14.2
" 7	7.4			5.6	337	834.9	202.3	632.6	0.61	5.23	8.5	7.5
" 8		150	1.030	5.8	199	529.9	215.0	314.8	0.36	1.79	4.9	+
" 9	7.2	130	1.029	6.0	209	313.9	208.7	105.1	0.35	1.43	4.0	0
" 10	7.2	115	1.027	6.2	242	202.5	191.0	11.4	0.30	1.62	5.3	0

Remarks — May 6: 6.26 gms. of Na Benzoate given in water by stomach tube. 0.764 gms. per kg. body weight. Urine greenish.
—May 7: Animal is very spastic and hypersensitive.

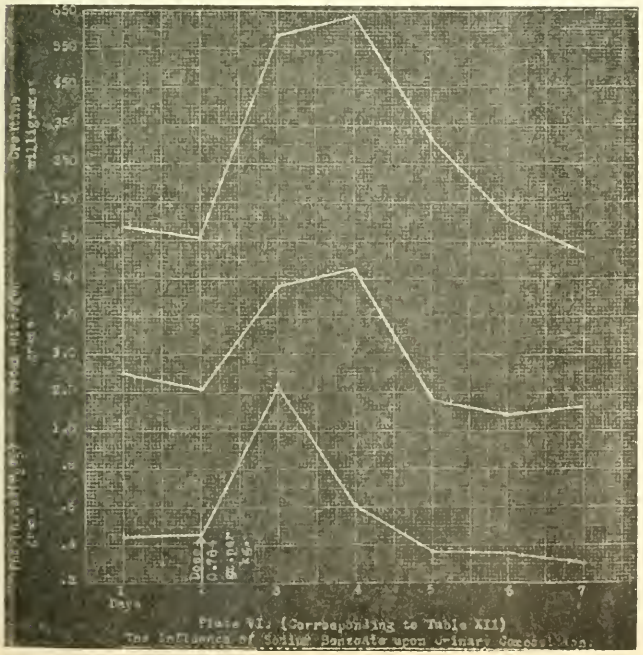


Plate VI. (Corresponding to Table XII)
The Influence of Sodium Benzoate upon Urinary Composition.

What is the source of this excessive nitrogen output, resulting from the ingestion of benzyl compounds or of benzoates? It is very improbable that much of it is contributed by the leucotoxic action of the benzyl radical. Some of it is due to the excretion of hippuric acid. The increase in the nitrogen eliminated is much greater than the amount of nitrogen output in the hippuric acid[44]. The excess nitrogen output persists for several days. Lewis[55] has shown that, in man, after the administration of from 6 — 10 grams of sodium benzoate, elimination as hippuric acid takes place very rapidly, 85 — 90 per cent of the ingested benzoate being excreted in from five to six hours. The rate of elimination of hippuric acid after the administration of sodium benzoate is only slightly less rapid than after the administration of hippuric acid[56]. Therefore the quantitative changes in nitrogen cannot be due altogether to hippuric acid excretion, because in many cases the nitrogen increased and the excess persisted for several days after the hippuric acid was, theoretically, eliminated.

With a single large dose of sodium benzoate the organism is unable to accomodate itself to the demands for conjugation, by normal glycocoll synthesis. The animal body can become accustomed to the presence in it of benzoic acid and react only to that extent to which the presence of a certain amount of benzoic acid at a given time compels the production of hippuric acid. When the benzoic acid feeding is extended over a prolonged period, the hippuric acid production reaches a definite level which is such that the extra nitrogen appearing in the urine is chiefly (at times entirely) in the form of hippuric acid[42]. But with a single large dose this acquired tolerance has not been established, and the excess nitrogen no doubt is due to the catabolism of protein tissues[35 44]. Epstein and Bookman declare that the increased catabolism occurs apparently only, (as evidenced by the increase in total nitrogen), when the fasting is prolonged[42]. This may explain the negative findings of Chittenden, Long and Herter, mentioned above, as they fed their patients. The rise in urinary nitrogen in a 15 kilogram dog was 100 per cent following the injection, intravenously, of 3.5 grams of sodium benzoate in 5 per cent aqueous solution as noted by Delprat and Whipple[43]. They state that the response to ingestion per os of sodium

benzoate is very much less than with the intravenous route, dosage of 0.4 gm. per pound of body weight being accompanied by an almost insignificant change in the urinary nitrogen.

There is no evidence to prove that the formation of hippuric acid itself within the body is harmful, but rather the secondary effects, resulting from its calling forth glycocoll from the proteins, must be regarded as the detrimental action.

The creatinuria induced here further strengthens the hypothesis of its indirect formation by benzoic acid action rather than by the benzyl grouping, as has been stated previously. Gibson and Martin[57] report no change in the creatine excretion following administration of 4 grams of sodium benzoate to cases of muscular dystrophy.

The Toxicity of Sodium Benzoate

Wiley observed that 1 to 2.5 grams of sodium benzoate given in capsules to humans causes gastric pain, vomiting and digestive disturbances. Meissner and Shepard in 1866 noted that nausea and vomiting were obtained in human beings with a dosage of 6 to 8 grams. Jaksch in 1897 declared that sodium benzoate may be tolerated without symptoms in doses up to 60 grams daily if given per os. The lethal dose intravenously has been given as 0.445 gram per pound of body weight[43], altho 1.7 gram per kilogram weight has been tolerated intravenously by dogs (Sollmann).

Kobert and Schulte declare the toxic effects on animals to be analogous to phenol; the gastric irritation, vomiting, dyspnea, decrease of reflexes, narcosis and sometimes convulsions.

The difficulties in administering sodium benzoate have been enumerated. A dosage of 0.761 gram per kilogram of body weight was employed, the drug being given in rather dilute aqueous solution. Shortly afterwards the animals vomited, and upon repeated administration, vomiting again ensued. Then, in one animal the requisite dose was incorporated within enteric capsules, but this was likewise followed by emesis, the vomitus being bile-stained. The animals were distinctly sick, their indisposition at this stage probably due entirely to the gastric irritation. On the following day the drug was mixed with a warm mucilaginous agar solution, retention then occurring after administration.

Eight hours later the dogs were noticed in convulsions. Their gait was very spastic, so much so that coordination was much affected. Reflexly the animals were so very hypersensitive that a light touch was sufficient to induce convulsions. These would apparently start with the jaw muscles, a movement similar to a yawn initiating the attack. Fine, fibrillary contractions would ensue, followed by clonic contractions, the hind legs going through movements as tho running, the front legs beating the air feebly and the head jerking spasmodically. The movements became weaker and weaker until they almost ceased, when opisthotonus would occur. There was a relaxation of the sphincters. One animal died, while the other survived and was utilized for the analyses.

A third dog, under similar dosage but with an aqueous solution, presented the same symptoms of gastric distress, and was prevented from vomiting by a mechanical arrangement. The same hypersensitiveness, fine tremors and spasticity were noted, but convulsions did not occur.

A subsidiary finding was that the blood calcium in these dogs, during their tetany like condition, was within normal limits.

Résumé

The urinary metabolites demonstrate that with all of these benzol derivatives, there is an increased catabolism; not the increase obtained with a stimulation of normal activity, but rather that which follows a toxic decomposition of body protein, which is also manifested here pharmacodynamically as depressant, antispasmodic and tone lowering.

If the benzyl radical had the above pharmacodynamic action, without causing a toxic decomposition of body protein, we would expect a lessened catabolic activity, since it has been proven that any means which diminishes the tonicity of the muscle also diminishes the creatine content[58]. The marked creatinuria negates this hypothesis.

The titratable acidity increases with the total phosphates. All of these changes, together with the augmentation of the nitrogen output (that is, the excess over the hippuric acid nitrogen) are due to the breakdown of tissue proteins. This is probably brought about indirectly by the acute demands for

conjugation by the benzoic acid. The theories as to how this is brought about (including the creatinuria) have been discussed elsewhere. This same urgent need is responsible for the formation of the glycuronic acid from the proteins.

Therefore we may say that metabolic action of these various benzyl compounds is due to the benzoic acid formed, rather than to the benzyl radical itself. Morover in noting the increased toxicity of sodium benzoate over benzyl benzoate and this in turn over benzyl succinate, we are able to conclude that the strength of the chemical reaction of the tissues is somewhat proportional to the rate at which benzoic acid is introduced into the organism. The benzol derivatives which possess a benzyl grouping must therefore hydrolyze to benzyl alcohol and then by oxidation to benzoic acid, the process entailing some time.

Phenylacetic and phenylpriopionic acids behave similarly, as, when they are introduced into mammals, they reappear in the urine conjugated with glycocoll, the phenylacetic as phenaceturic and the phenylpropionic, having been oxidized to benzoic, as hippuric acid[59]. Hijikata[60] noted an increase in the total nitrogen, urea and ammonia after administration of these acids to rabbits, not only when maintained in nitrogen balance but with fasting animals. The increase in the ammonia, even tho the acids were neutralized, favors the view that the simultaneous increases in the quantities of total nitrogen and urea excreated may have been due to a pathological decomposition of tissue proteins.

None of the benzol derivatives modified the creatinine excretion. We can say with McCollum and Hoagland[35] that endogenous protein metabolism appears to consist of two types. One can be stimulated greatly for ammonia production by the introduction of mineral acids, or for hippuric acid when benzoic acid is introduced; the other, measured by creatinine remains unaffected by the methods described.

Conclusions

(1) Judging from experimental investigations in dogs, the therapeutic dose of benzyl benzoate for human beings is probably insufficient to disturb the normal nitrogenous metabolism.

(2) Larger doses, that is, above ½ c. c. per kilogram of body weight, bring about an increase of protein catabolism in dogs. The titratable acidity and total phosphate excretion in the urine are augmented. The total nitrogen output is increased. A marked creatinuria occurs. Conjugated glycuronates appear in the urine. Creatinine metabolism is unmodified.

(3) The changes that occur are probably brought about by benzoic acid, either when introduced as benzoates or by conversion from the benzyl grouping.

(4) Benzyl succinate produces less change in the normal nitrogenous metabolism of the dog than the other benzol derivatives investigated.

(5) Benzyl succinate produces less change in the normal employed.

(6) A new ester, di-benzyl succinate is suggested for pharmacological investigation.

(7) Several theories are submitted relative to the catabolic processes that ensue following the administration of these benzol derivatives.

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THE INFLUENCE ON METABOLISM OF SOME PURINE AND PYRIMIDINE BASES.

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The present communication is an extension of the investigations conducted by Whipple, Underhill and others on the intoxication and changes in metabolism brought about by certain of the cleavage products of protein. Ringer and Underhill[1] have pointed out that all proteins, except gelatin, when introduced parenterally into dogs induce a marked effect on nitrogenous metabolism. On the other hand the amino acids are without this influence. It is also stated by them that certain of the nucleic acids are capable of producing this catabolic effect to a very marked degree.

Inasmuch as nucleic acid, especially yeast nucleic acid, has a marked influence upon nitrogenous metabolism it was of interest to determine whether derivatives of nucleic acid produce similar effects. The substances investigated were uracil, caffein, theobromine, hypoxanthine and uric acid.

Methods: The plan followed was to determine daily the excretion of urinary nitrogen, creatinine, creatine and phosphates. Urine was marked off in 24-hour periods in fasting rabbits by compression of the bladdar. In order that the plane of nitrogenous metabolism should reach a uniform level the animals were allowed to fast for two days previous to administration of the substance to be investigated. The substance was dissolved in physiological salt solution with just sufficient addition of alkali to cause solution and slowly injected into an ear vein. Two control experiments were carried through to determine the influence of the solvent upon the excretion of the substances described above. One animal received 20 cc. of 0.9 per cent. sodium chloride solution made

* These data are taken from the thesis of Dr. H. F. Farrell presented in candidacy for the degree of Doctor of Medicine, Yale University, 1922.

alkaline with 10 per cent. sodium hydroxide (1.5 cc. sodium hydroxide solution to 98.5 cc. 0.9 per cent. sodium chloride solution). The second animal received 30 cc. of the same solution. Since the changes in urinary excretion under the experimental conditions of starvation and solvent injection varied insignificantly from starvation figures alone the data are omitted.

The Influence of Pyrimidine and Purine Derivatives upon Urinary Composition in the Rabbit.

Uracil. In Tables I and II are presented the data obtained after intravenous injection of uracil. The figures show that inconstant effects are to be expected. Thus in Rabbit "R" a significant increase in the total nitrogen excretion occurred whereas little change is to be observed with Rabbit "B".

The Purine Bases. From Tables III to XI inclusive it may be seen that caffeine, theobromine, hypoxanthine and uric acid all possess the property of inducing significant changes in urinary composition which may be taken as indications of stimulated catabolism.

TABLE I.

The Influence of Uracil upon the Composition of the Urine.
Rabbit "A" — Body Weight 2.6 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gms.	gm	gm
July 19	210	150	1.010	Acid	.780	.017	.081	.140
" 20	40	60	1.015	Acid	.795	.021	.076	.218
" 21	85	240	1.010	Acid	1.098	.026	.093	.246*
" 22	50	50	1.018	Acid	.720	.017	.071	.204
" 23	50	115	1.012	Acid	.630	.011	.063	.102

* The asterisk marks the urine of the first day after injection.

TABLE II.

The Influence of Uracil upon the Composition of the Urine.
Rabbit "B" — Body Weight 2.0 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
July 26	150	60	1.014	Acid	.738	.023	.080	.082
" 27	210	180	1.010	Acid	.792	.023	.075	.148
" 28	60	110	1.012	Acid	.820	.034	.074	.099*
" 29	95	70	1.010	Acid	.540	.013	.070	.117
" 30	30	40	1.012	Acid	.396	.010	.057	.120

* The asterisk marks the urine of the first day after injection.

TABLE III.

The Influence of Caffeine upon the Composition of the Urine.

Rabbit "A" — Body Weight 2.1 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Aug. 7	206	158	1.010	Acid	.540	.017	.107	.245
" 8	226	225	1.007	Acid	.600	.027	.095	.275
" 9	450	420	1.005	Acid	1.140	.029	.114	.350*
" 10	450	445	1.005	Acid	1.020	.024	.086	.285
" 11	450	350	1.008	Acid	1.020	.068	.065	.275
" 12	450	450	1.005	Acid	.840	.052	.061	.300

* The asterisk marks the urine of the first day after injection.

TABLE IV.

The Influence of Caffeine upon the Composition of the Urine.

Rabbit "B" — Body Weight 2.6 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Aug. 23	200	75	1.016	Acid	.828	.024	.108	.195
" 24	150	100	1.012	Acid	.846	.061	.071	.270
" 25	290	225	1.012	Acid	1.125	.070	.112	.290*
" 26	190	125	1.010	Acid	1.044	.019	.059	.270
" 27	190	115	1.010	Acid	.990	.027	.056	.270

* The asterisk marks the urine of the first day after injection.

TABLE V.

The Influence of Theobromine upon the Composition of the Urine.

Rabbit "A" — Body Weight 1.8 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Aug. 9	150	100	1.012	Acid	.738	.007	.089	.153
" 10	150	120	1.000	Acid	.738	.003	.085	.216
" 11	160	175	1.008	Acid	.918	.035	.094	.264*
" 12	230	225	1.007	Acid	.972	.029	.064	.285
" 13	225	265	1.006	Acid	.930	.011	.031	.315

* The asterisk marks the urine of the first day after injection.

TABLE VI.

The Influence of Theobromine upon the Composition of the Urine.

Rabbit "B" — Body Weight 2.3 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Aug. 23	300	200	1.007	Acid	.810	.018	.098	.230
" 24	300	275	1.006	Acid	.960	.017	.109	.300
" 25	300	280	1.006	Acid	1.050	.024	.120	.325*
" 26	300	260	1.005	Acid	1.140	.013	.051	.310
" 27	300	275	1.005	Acid	1.050	.009	.052	.310

* The asterisk marks the urine of the first day after injection.

TABLE VII.

The Influence of Uric Acid upon the Composition of the Urine.

Rabbit "A" — Body Weight 2.1 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Oct. 7	50	50	1.030	Acid	.864	.023	.068	.114
" 8	170	150	1.012	Acid	1.026	.024	.073	.201
" 9	80	115	1.015	Acid	1.260	.052	.069	.225*
" 10	50	50	1.020	Acid	1.080	.014	.061	.215

* The asterisk marks the urine of the first day after injection.

TABLE VIII.

The Influence of Uric Acid upon the Composition of the Urine.

Rabbit "B" — Body Weight 2.6 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Oct. 11	300	275	1.008	Acid	1.230	.032	.087	.275
" 12	300	325	1.006	Acid	1.320	.056	.087	.325
" 13	125	250	1.008	Acid	1.890	.066	.122	.450*
" 14	100	75	1.018	Acid	1.260	.043	.070	.312

* The asterisk marks the urine of the first day after injection.

TABLE IX.

The Influence of Uric Acid upon the Composition of the Urine.

Rabbit "C" — Body Weight, 1.7 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Oct. 21	150	75	1.020	Acid	.900	.014	.051	.300
" 22	175	75	1.018	Acid	.900	.038	.054	.375
" 23	150	75	1.015	Acid	1.230	.051	.055	.415*
" 24	125	95	1.010	Acid	1.125	.047	.051	.325

* The asterisk marks the urine of the first day after injection.

TABLE X.

The Influence of Hypoxanthine upon the Composition of the Urine.

Rabbit "A" — Body Weight 2.0 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Oct. 28	100	50	1.022	Acid	.945	.009	.085	.168
" 29	100	60	1.021	Acid	1.050	.017	.076	.230
" 30	75	70	1.022	Acid	1.200	.101	.094	.278*
" 31	85	55	1.023	Acid	1.215	.090	.017	.278

* The asterisk marks the urine of the first day after injection.

TABLE XI.

The Influence of Hypoxanthine upon the Composition of the Urine.

Rabbit "B" — Body Weight 1.8 kgm.

Date	Water Intake	URINE. Vol.	Sp. Gr.	Reaction to Litmus	Total N	Creatine	Creatinine	Phosphates
1921	cc.	cc.			gm	gm	gm	gm
Oct. 28	300	225	1.005	Acid	.738	.020	.052	.135
" 29	300	275	1.005	Acid	.984	.026	.066	.260
" 30	300	275	1.006	Acid	1.152	.045	.075	.296*
" 31	300	325	1.004	Acid	.900	.022	.077	.288

* The asterisk marks the urine of the first day after injection.

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STUDIES OF THE VITAMINE OF COD LIVER OILS.

I. The Potency of Crude Cod Liver Oil, Pressed Cod Liver Oil and Cod Liver Stearin.

By ARTHUR D. HOLMES

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The purpose of the experiments discussed below was to secure quantitative data concerning the vitamine potency of commercial cod liver oil. A series of experiments was made with crude cod liver oil, pressed cod liver oil and cod liver stearin. In each series of tests four growing albino rats received a known daily feeding of oil which varied in amounts for the different animals. Approximately the same amounts of the different oils were fed in the different series of tests. Detailed data concerning the food intake and change of body weight of experimental animal are reported graphically below. The results obtained show that crude oil, pressed oil, and the stearin all have a relatively high vitamine potency and that pressed oil is most potent.

Medicinal cod liver oil is obtained by "cold pressing" high grade crude cod liver oil that has been prepared by rendering fresh cod livers under carefully controlled conditions. By the "cold press" process, about 80% of the crude cod liver oil is converted into "pressed oil" and 20% remains as cod liver stearin, a by-product of low commercial value principally used by soap manufacturers. After the "pressed oil" is filtered it becomes "medical cod liver oil" without further treatment.

The investigations of Zilva[1], McCollum[2], Shipley[3] and others supply sufficient evidence to indicate that cod liver oil has the highest vitamine "A" potency of any substance thus far studied. In view of this fact it is of considerable interest from a commercial as well as a scientific standpoint to secure data relative to the vitamine "A" potency of both products, pressed cod liver oil (medicinal cod liver oil) and cod liver stearin, obtained in the manufacture of medicinal cod liver oil and it

was for the purpose of securing such data that the experiments reported here were undertaken.

In order that it should be possible to compare the color of commercial products manufactured in this locality, crude oil was obtained from one of the rendering stations which are conveniently located to receive fresh livers from the near shore fishermen. It was arranged that during the regular refining process, samples of crude oil, pressed oil and cod liver stearin should be reserved for experimental purposes and it is believed that these samples were representative of the ordinary commercial products. Also special care was exercised to obtain samples of pressed oil and cod liver stearin from the same source as the crude oil sample, so that at least quantitative data could be secured concerning the relative vitamine "A" potency of crude oil, pressed oil and cod liver stearin.

An analysis of the commercial oils discussed in this paper gave the following information concerning their characteristics:

CHEMICAL AND PHYSICAL CHARACTERISTIC OF COMMERCIAL COD LIVER OILS.

	Crude Cod Liver Oil	Pressed Cod Liver Oil	Cod Liver Stearin
Specific Gravity at 25°C....	0.9212	0.9234	0.9164
Refractive Index at 20°C....	1.4790	1.4793	1.4736
Iodine Number (Hanus)....	150.4000	160.0000	117.7000
Saponification value.....	185.4000	185.7000	190.4000
Acid value	4.8770	4.5370	10.8500
Cold Test (Clouding Point).	12°C.	6°C.	25°C.

In order that it should be possible to compare the color of the oils reported here with each other and with those to be reported later, a colorimeter analysis was made with the following results:

RESULTS[1] OF COLORIMETRIC ANALYSIS[a] OF COMMERCIAL COD LIVER OILS.

Commercial crude cod liver oil.....	35 yellow 12 red
Commercial pressed cod liver oil.....	35 yellow 4 red
Commercial cod liver stearin.....	66 yellow 43 red

[a] The above analyses were made with Lovibond scale.

1 The author is indebted to Dr. David Wesson and Herbert S. Bailey of the Southern Cotton Oil Company for the above data concerning the color of cod liver oils.

The animals used for these experiments were albino rats purchased from a dealer who supplied no information concerning the relationship, if any existed, between the different animals. The thirteen animals reserved for the experiments discussed below were divided into three groups and the individual members of the groups were so chosen that each group consisted of average male and female animals and accordingly each group was believed to be representative of the entire lot. The animals were originally purchased for breeding purposes and so for a time were fed the usual stock diet which consisted of dog biscuit and skimmed milk reconstituted from a commercial skimmed milk powder. As a result of a change in the laboratory program, these animals averaging less than 75 gm. in weight were shifted to the experimental diet, which was free from fat-soluble vitamine.

The experimental diet consisted of casein 18%, cottonseed oil 22%, salt mixture 4%, cornstarch 28% and milk sugar 28%. The casein was prepared by precipitation from reconstituted skimmed milk made with a commercial skimmed milk powder. The casein was subsequently purified by the usual methods. The cornstarch, cottonseed oil, which was after a time replaced by a peanut oil, and the milk sugar were taken from the supply maintained for manufacture of pharmaceuticals. The salt mixture was prepared in accordance with the data reported by Osborne and Mendel[4]. As a result of a thorough mixing of the above ingredients, a paste was obtained which was conveniently fed to the rats in a small circular dish of about 10 gm. capacity. The food was replenished and weighed daily and the animals were weighed on Mondays, Wednesday and Fridays. To meet the body requirements for vitamine "B" a 0.2 gm. tablet of dried brewer's yeast was fed to each animal daily.

In view of the high vitamine content of cod liver oils, it appeared desirable to dilute the cod liver oils under consideration with a vitamine free oil in order to facilitate quantitative estimation of their vitamine potency. Accordingly for the purpose of these experiments the crude and the pressed oils and the cod liver stearin were each diluted with eleven parts of peanut oil. The peanut oil was from the same lot as that included as an ingredient of the experimental diet discussed above . The dilute oils were added to the diet by means of a

calibrated medicine dropper and to avoid possible contamination a dropper was permanently assigned to each individual oil mixture being studied.

When the addition of the cod-liver-oil-peanut-oil mixture to the diet of the failing animals was first attempted, considerable difficulty was experienced in getting the animals to eat the oil mixture which was placed in a separate container. In fact, in most cases, they refused to touch it, so for a few days the oil mixture was administered by dropping it into the animals' opened mouth, but this was too time-consuming and required considerable dexterity to avoid dropping the oil outside rather than inside the animal's mouth. Noting the unusual avidity with which the animals consumed the yeast tablets that had regularly formed a part of the experimental diet, the oil mixture was added to the yeast tablets by crushing the tablets in small very shallow porcelain dishes and allowing them to absorb the oil mixture. In some instances it was found necessary for the first feeding to add a second yeast tablet to get the rat to eat the yeast-oil combination, but thereafter they always anticipated the yeast and oil with great eagerness and ate it at once with great avidity.

In view of the evidence which has been submitted by the numerous investigators concerning the effect of sunlight as a corrective for a rickets-producing diet, it seems desirable to include data relative to the lighting condition of the colony room in order that other investigators may be able to make comparisons concerning this factor. Our colony of experimental animals is located in the second floor room of a concrete building which is lighted on the west, north and east sides. The glass area approximating 28% of the total wall space, is almost equally divided on three sides. The east side is of wire-fire glass. The north and west windows are of clear glass. The upper half of the west windows are curtained with greenish yellow curtains.

The accompanying charts, blue-prints of which are available for distribution, supply detailed data concerning the variation in the body weight of the experimental animals and the food consumed by them during the test period. The curves reporting the amount of food eaten indicate the total food intake for periods of five days each. On referring to charts it will be noted that no "normal" growth curves have been

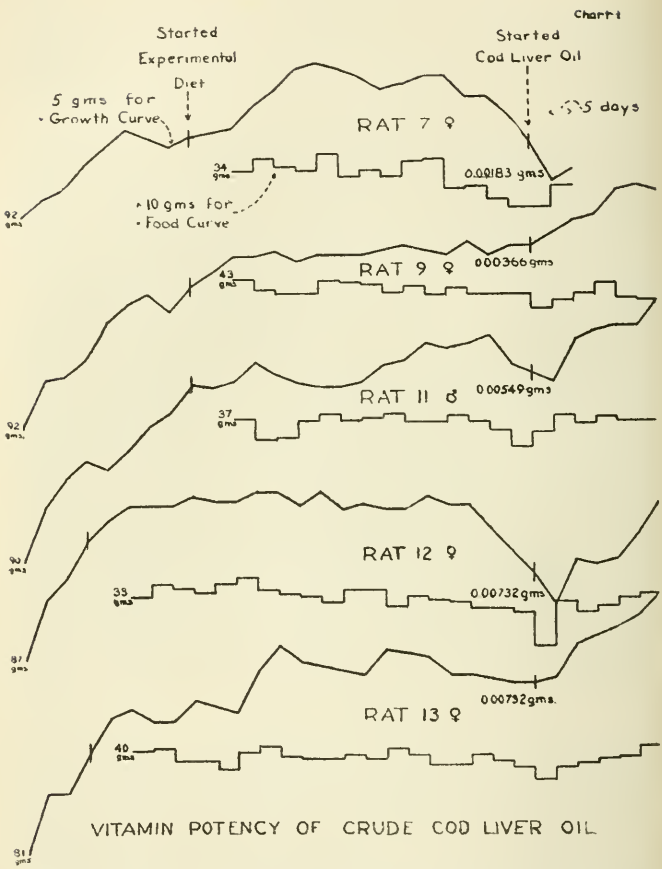
included, since no data was obtained from the breeder concerning the normal rate of growth of this strain of animals.

Crude Cod Liver Oil

Of the five animals fed crude cod liver oil, No. 7 daily received one drop, 1/12 of this or 0.00183 gm. being cod liver oil and was unable to recover from its condition of malnutrition. The rate of body increase for rat No. 9, which received two drops, (.00366 gm. of cod liver oil), for rat No. 11 which received three drops, (.00549 gm. of cod liver oil), for rat No. 12 which received four drops (.00732 gm. of cod liver oil) and for rat No. 13 which received four drops, (.00732 gm. of cod liver oil) is so near No. 13 which received four drops, (.00732 gm. of cod liver oil) is so near identical that it would appear that two drops (.00366 gm. of cod liver oil) of the diluted oil is sufficient to meet the body requirements for this type of animal. The growth curve of rat No. 12 is of more than usual interest since this animal had fallen to such a precarious physical condition that for three days it ate none of its food and maintained the characteristic position of approaching death. During that time it was fed four drops of the cod liver oil mixture daily by means of a medicine dropper introduced into its mouth. In view of this condition the eventual recovery and subsequent increase in body weight supplies quite definite evidence of the efficacy of cod liver oil in alleviating malnutrition resulting from an inadequacy of vitamine "A" in the diet.

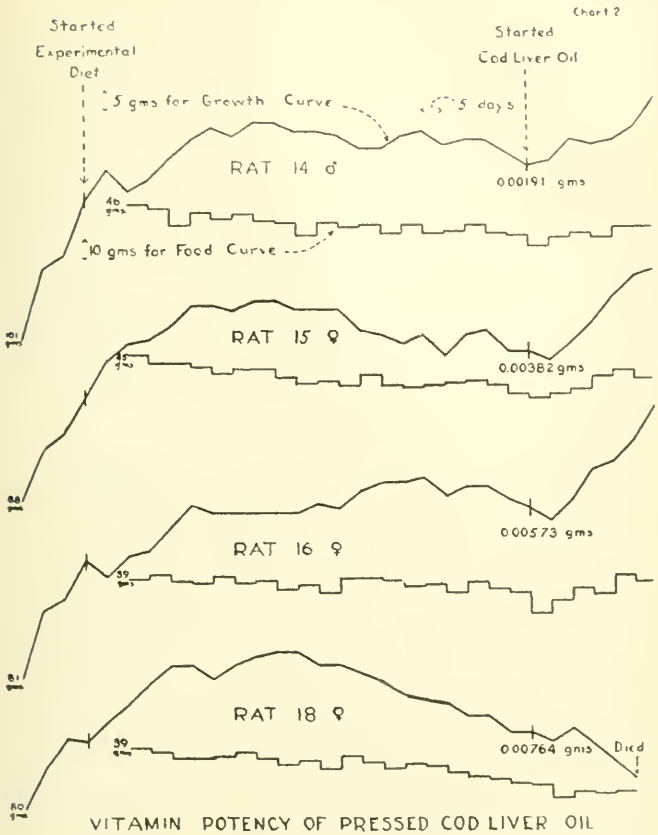
Pressed Cod Liver Oil

Of the four animals fed pressed cod liver oil, rat No. 14 received one drop (.00191 gm. of cod liver oil), rat No. 15 received two drops (.00382 gm. of cod liver oil), and No. 16 received three drops (.00764 gm. of cod liver oil) daily, it appears that for these particular animals one drop of the diluted oil was practically as adequate for the body needs as the larger quantities. Inasmuch as no postmortem was made of rat No. 18, which died during the experiment, no information is available as to the exact cause of death. It is felt however, that the failure of this rat, which was receiving four drops of cod liver oil daily, to respond to the treatment was in all prob-



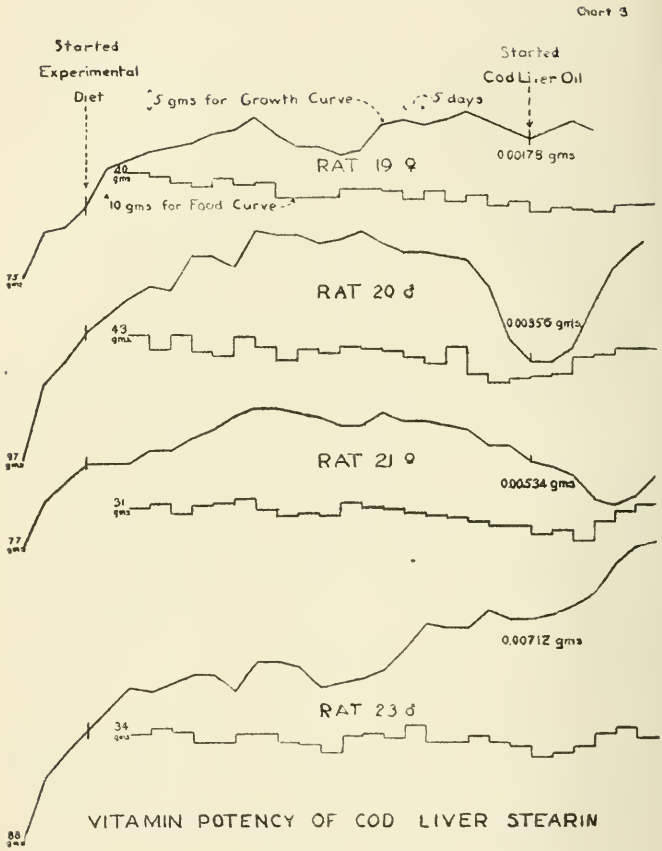
ability due more to the individuality of the animal than to the nature of the diet it received, especially since it received much more of the oil than the others which exhibited such a marked improvement.

Animals Nos. 19, 20, 21 and 23 were fed cod liver stearin. Rat No. 19 received .00178 gm. of cod liver stearin daily and



Cod Liver Stearin

the resulting data indicate that this amount of stearin is just about sufficient to enable an albino rat to maintain its body weight. Animal No. 20 was fed .00356 gm. of stearin, which was apparently sufficient to meet the body needs for growth since the subsequent body increment of this animal compares



very favorably with that of the animals number 21 and 23, which received .00534 gm. and .00521 gm. of stearin respectively. It should be noted however, in referring to the curve of rat No. 21 that previous to the addition of cod liver stearin to the diet, this animal developed a very severe diarrhea. For a time the excretion consisted wholly of a very offensive watery mu-

cus, but after the animal had been fed cod liver stearin fourteen days, it recovered from this condition and increased its body weight very materially. It would seem from the data obtained with this group of experimental animals that the cod liver stearin, resulting from the manufacture of cod liver oil, contains very appreciable quantities of the fat-soluble vitamine. In this connection it is interesting to note the findings of Zilva and Miura[5] who report that crude cod liver oil was more potent than pressed cod liver oil in vitamine "A", and the conclusions of Zilva and Drummond[6] who report "little vitamine being removed in the stearin", but as these investigators supply no information concerning the characteristics of their "stearine", it is impossible to judge whether their product was comparable with that studied in this investigation which was pure white stearin, "cold pressed", from number one medicinal cod liver oil.

Summary

Thirteen experiments were conducted to determine the relative vitamine "A" potency of crude cod liver oil, pressed cod liver oil and cod liver stearin.

The oils discussed above were prepared by the usual commercial process and all were obtained from the same crude oil.

The tests were conducted with albino rats, maintained under standardized conditions as regards diet, light, and experimental procedure, the method of administering the oils being investigated.

The results of the three series of tests to determine the vitamine potency of crude cod liver oil, pressed cod liver oil, and cod liver stearin show that all are capable of meeting the body requirements for vitamine "A" of growing albino rats. Considering the different series of tests as groups, the results show that pressed cod liver oil has a higher potency than that of the crude oil or the stearin. While the above tests show that in one instance at least as little as 0.00366 gm. of crude oil, 0.00191 of pressed oil, and 0.00356 gm. of stearin was sufficient to promote satisfactory growth, much more extensive data are required to furnish conclusive evidence concerning the minimum amount of these oils necessary to supply an adequate amount of vitamine "A" for the dietary needs of the growing albino rat.

Coincident with the above tests attention has been given to other factors influencing the vitamine potency of cod liver oils and it is expected that results of these tests will be reported in the very near future.

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SUMMARY OF PUBLICATIONS ON INSULIN TO DATE

Dr. Frederick G. Banting first conceived the idea of preparing a potent extract from the atrophied pancreas, and carried it out successfully in collaboration with C. H. Best. Later, J. B. Collip, E. C. Noble, J. Hepburn and J. K. Latchford became associated in the work. The experiments on animals were conducted in the Department of Physiology of the University of Toronto under the direction of Professor J. J. R. Macleod, and received the aid and support of Professor V. E. Henderson of the Department of Pharmacology, on whose staff Banting held an appointment. The clinical application was then made, with the assistance of W. R. Campbell and A. A. Fletcher, in the clinic of Professor Duncan Graham in the Toronto General Hospital and in other institutions. Through the support of the Connaught Laboratories, under the direction of Prof. J. G. Fitzgerald and Prof. R. Defries, facilities were obtained for the first small production for clinical trials, with insulin prepared by a method elaborated by C. H. Best and J. B. Collip. The rapid and brilliant achievements bear witness to the genius and energy of the young investigators and the experience and skill of their older advisors and associates.

As the discovery of an effective non-toxic pancreatic extract is literally epoch-making, and as few readers have easy access to all the journals in which the early papers have appeared, a useful purpose may be served by the following abstract of all the publications on this subject up to the present. Thanks are due to the various journals for permission to quote much of these papers *verbatim*.

Banting, F. G. and Best, C. H. *The internal secretion of the pancreas. Journal of Laboratory and Clinical Medicine*, 7, 1922, 251-256.

"The hypothesis underlying this series of experiments was first formulated by one of us in November, 1920, while reading an article dealing with the relation of the isles of Langerhans to diabetes. From the passage in this article, which gives a resume of degenerative changes in the acini of the pancreas following ligation of the ducts, the idea presented itself that since the acinous, but not the islet tissue, degenerates after this operation, advantage might be taken of this fact

to prepare an active extract of islet tissue. The subsidiary hypothesis was that trypsinogen or its derivatives was antagonistic to the internal secretion of the gland. The failures of other investigators in this much-worked field were thus accounted for.

"The feasibility of the hypothesis having been recognized by Professor J. J. R. Macleod, work was begun under his direction in May, 1921, in the Physiological Laboratory of the University of Toronto."

Chart I shows the first experiments with injection of pancreatic extract intravenously, in the terminal period of diabetes following removal of the pancreas in two stages. The increase of blood and urine sugar after oral administration of 25 gm. glucose was markedly inhibited by intravenous injection of 4 cc. of extract of atrophied dog pancreas.

"We first ligated, under general anesthesia, the pancreatic ducts in a number of dogs. (Blood sugar estimations on these animals were recorded from time to time. We have no record of a hyperglycemia).

"The extract was prepared as follows: The dog was given a lethal dose of chloroform. The degenerated pancreas was swiftly removed and sliced into a chilled mortar containing Ringer's solution. The mortar was placed in freezing mixture and the contents partly frozen. The half frozen was then completely macerated. The solution was filtered through paper and the filtrate having been raised to body temperature, was injected intravenously.

"We performed several experiments with the object of exhausting the zymogen granules of the pancreas. Prolonged secretin injections and vagus stimulation below the diaphragm were practiced. Fortune favored us in the first experiment. In subsequent attempts we were never able to exhaust the gland sufficently to obtain an extract free from the disturbing effects of some constituent of pancreatic juice."

The chart for July 27 shows the effect produced on the percentage of blood sugar and on the sugar excretion by the oral administration of twenty-five grams of dextrose in 250 cc. of water. At 10 A. M. July 30, the percentage of blood sugar was 0.20. Four cc. of extract of degenerated pancreas were injected intravenously. At 11 A. M. the blood sugar had fallen to 0.12 per cent. The injections of extract are shown in the chart. At 12 A. M. twenty grams of sugar in 200 cc. of water were given by stomach tube. The chart records the effect."

"Chart II is the record of dog 92, weight 11.9 kg. A complete pancreatectomy was performed on this animal at 3:00 P. M., August 11. The first injection of extract was given 6 hours after the operation and subsequently an injection every four hours. This extract was freshly prepared from a 10 kg. dog, whose pancreatic ducts had been ligated for ten weeks. 125 cc. of extract were prepared from the gland residue.

"On August 12, the blood sugar curve shows that neither five nor eight cc. of this extract every four hours were sufficient to counterbalance the upward trend of the percentage of sugar of the blood. At 10 P. M. the dose was increased to 12 cc. and a marked fall is noted. The chart at 10 A. M. August 14 records the reduction of the

percentage of sugar in the blood below its normal level, as a result of extract from another degenerated gland. (The exceptionally higher values for the volume of urine and the urinary nitrogen for August 15 and 16 may be due to the adulteration of the urine with vomit). On August 15 at 10 A. M. the chart shows the effect produced by ten cc. of the same gland extract made 0.1 per cent acid with HCl. This extract made 0.1 percent alkaline with NaOH causes a slight reduction (August 15, 8 P.M.). The effect may be due to the alkali."

Extracts of normal dog pancreas were found to reduce blood sugar, but were less potent than extracts of atrophic glands and were decidedly toxic. Somewhat similar results are described with extracts made after exhaustion of the pancreas by secretin and vagus stimulation. Chart 3 presents the following experiment:

"The normal blood sugar of dog 408 was .090 per cent. Eighteen hours after pancreatectomy the percentage of sugar in the blood was .27. Twenty-two hours after the operation, 1 P. M. August 4, the blood sugar was .26 percent. During the twenty-two hours 3.10 gms. of sugar were excreted. The volume of urine was 494 cc. At one P. M. we administered five cc. of extract of degenerated pancreas which had been prepared four days previously and kept in cold storage. At two P. M. the blood sugar was .16 per cent. At three P. M. the percentage of sugar in the blood had fallen to .15. From one the three P.M. .15 grams of sugar were excreted in a volume of twenty-six cc. of urine. Three and forty-three hundredths gms. of urinary nitrogen were excreted in the twenty-four hours following the operation. The G. to N. ratio for this period was 1.4:1. From 3 P. M. to 7 P. M. the percentage of sugar in the blood shows a gradual rise from .15 to .25 per cent. The latter level was maintained until 9 P. M. The chart shows a slight rise in sugar excretion following the rise of blood sugar. At 9 P. M. five cc. of extract which had been exposed to room temperature for one hour was injected intravenously. The blood sugar was reduced to a value of .18 per cent. The chart shows a gradual ascent from this value to .27 per cent. At 10 P. M. the percentage of sugar in the blood was .27. At this hour five cc. of extract of liver, prepared in precisely the same manner as the pancreatic extract, were administered intravenously. One hour later the blood sugar was .30 per cent. This level was maintained during the following three hours. It was unaffected by an injection of 5 cc. of extract of spleen. The chart shows the rise in volume of urine and amount of sugar excreted. At 2 P. M. (blood sugar .3 per cent) five cc. of an extract of degenerated pancreas were injected. A sharp fall in the blood sugar resulted. At 3 P. M. and again at 4 P. M. a similar dose of extract was given. The chart records the lasting effect. The 2 P. M. level of .30 per cent was regained twelve hours after the first injection. The hourly excretion of sugar ran approximately parallel with the percentage of sugar in the blood. Between 1 P. M. and 2 P. M. .52 gms. were excreted. Less than .02 gms. were excreted between 7 P. M. and 8 P. M. The highest glucose to nitrogen ratio observed in this experiment was a 3:1 value for the 22 hour interval between 2 P. M.

the sixth of August and noon the following day. At 12 noon August 6 the percentage sugar in the blood was .40 percent. Five cc. of boiled extract of degenerated pancreas was injected intravenously at this stage and caused no reduction of blood sugar. At twelve midnight, August 6, five cc. of extract of degenerated pancreas which had been prepared 48 hours previously were administered. The blood sugar fell from .43 per cent at 12 P. M. to .37 per cent at 1 A. M. Five cc. doses were given at 1, 2 and 3 A. M. and a twenty-five cc. dose at 4 A. M. The chart shows the reduction in blood sugar to a normal level and the beginning of an upward trend five hours after the last injection of extract. The animal died at 12 A. M. August 7."

"Chart 4, Dog 9, gives additional evidence on several important points which have been referred to previously. At 6 P. M., September 8, we administered ten cc. of extract of degenerated pancreas *per rectum*. There was no reduction in blood sugar at 7 P. M. when we gave 12 cc. of extract of exhausted gland intravenously. The chart records the effect of this and subsequent injections of the same material. At 6 A. M., September 10, we administered 15 cc. of extract of exhausted gland per rectum. There was no effect. At 8 A. M. September 10, fifteen cc. of extract of exhausted gland were injected intravenously. The drop in blood sugar was very marked. Twenty cc. of exhausted gland extract, made 1 per cent alkaline with NaOH, were incubated three hours at body temperature with 10 cc. of active pancreatic juice. This solution was neutralized and injected intravenously at 7 P. M. September 10. No reduction in blood sugar resulted. At 2 P. M. September 11, 20 cc. of acid extract, incubated for three hours at 37.5° C. were injected. The curve shows the drop in blood sugar. On September 13 at 9 A. M. and 2 P. M. the effect of extracts from the partially exhausted gland of a cat is shown. The extract produces a pronounced general reaction.

"We observe that extracts prepared from these more or less exhausted glands, while retaining to some extent the reducing effect upon blood and urine sugar, produce many symptoms of toxicity which are absent after injections of extracts from completely degenerated glands."

"In the course of our experiments we have administered over seventy-five doses of extract from degenerated pancreatic tissue to ten diferent diabetic animals. Since the extract has always produced a reduction of the percentage sugar of the blood and of the sugar excreted in the urine, we feel justified in stating that this extract contains the internal secretion of the pancreas."

"The results of the experimental work reported in this article may be summarized as follows:

"Intravenous injections of extract from dog's pancreas, removed from seven to ten weeks after ligation of the ducts, invariably exercise a reducing influence upon the percentage sugar of the blood and the amount of sugar excreted in the urine .

"Rectal injections are not effective.

"The extent and duration of the reduction varies directly with the amount of extract injected.

"Pancreatic juice destroys the active principle of the extract.

"That the reducing action is not a dilution phenomenon is indicated by the following facts: (1) hemoglobin estimations before and after administration of extract are identical; (2) injections of large quantities of saline do not affect the blood sugar; (3) similar quantities of extracts of other tissues do not cause a reduction of blood sugar.

"Extract made 0.1 per cent acid is effectual in lowering the blood sugar.

"The presence of extract enables a diabetic animal to retain a much greater percentage of injected sugar than it would otherwise.

"Extract prepared in neutral saline and kept in cold storage retains its potency for at least seven days.

"Boiled extract has no effect on the reduction of blood sugar."

Banting, F. G. and Best, C. H., *Communication to the Academy of Medicine* (Toronto), February 7, 1922.

After a summary of the early work as above reviewed, the authors continue:

"The results so far reported occupied our time until the middle of November, 1921, when a new era was introduced by the discovery that the foetal calf pancreas of under five months' development did not contain pancreatic juice, but did contain internal secretion."

"Foetal calf extract was prepared by macerating the glands in Ringer's solution and filtering until a clear solution was obtained. To get an idea of the potency of the extract so obtained, we placed 50 gm. of tissue in 250 cc. of saline, macerated and filtered; 15 cc. of this solution were then diluted to 250 cc. with saline. A 15 cc. dose of this solution reduced the percentage of blood sugar in a 10 kg. dog from .40% to .15% in three hours.

"Up to this time the extract had been given intravenously. We found that this extract when given subcutaneously gave a slower and more prolonged, but not less marked, fall in the percentage of blood sugar.

"In the endeavor to secure a sterile extract, we next tried the effect of preservatives. We found that a .7% tricresol, which is double the strength used in preserving Diphtheria Anti-toxin, did not interfere with the active principle. It was also found that the extract could be Berkfeldted, but much of its potency was lost in this procedure.

"Alcohol was then tried in the place of saline, as an abstractive, and it was found that the active principle was soluble. This was an important fact, for it led us to believe that by the use of alcohol we could extract the active principle from the whole gland. Consequently we macerated a whole beef pancreas immediately after the death of the animal in 95% alcohol. After allowing it to stand for 12 hours, the liquid was squeezed out and filtered until clear. This solution was then evaporated to dryness in a warm air current. The resin-like residue was re-dissolved in saline and injected subcutaneously into a diabetic dog. The percentage of blood sugar fell from .35 to .08 in three hours and the urine became sugar free. This was repeated with

similar results. We had thus obtained from the whole gland an extract of the active principle which, when washed with toluol, gave a brownish powder, which could be kept sterile, which was soluble in saline, and which in minute doses (50 mg.) gave a pronounced effect on the blood sugar.

"At this stage of the investigation, we secured the services of Dr. Collip, Professor of Biochemistry at Edmondton University on a year's leave of absence. He has worked intensively and has now obtained a very potent, soluble, protein-free extract which is being tested clinically.

"Previous to this we had anesthetized and connected a diabetic dog to a blood pressure recorder. It was found that the protein containing extract had a temporary but marked depressor effect. Samples of blood were taken every half hour during the experiment and it was found incidentally that the percentage of blood sugar fell but slightly following the injection of a known potent extract. This fact may, in part, account for the failures of some observers to obtain results.

"The question now arose as to why the extract acted but slightly under anesthesia. It seemed reasonable to suspect that the glycogenetic function of the liver was in some way involved, as glycogen is not built up during anaesthesia. We cannot state definitely, but some of our results would lead us to believe that the presence of the internal secretion of the pancreas is necessary in order that the liver build up glycogen from sugar."

Mention is next made of attempts to prolong the lives of totally depancreatized dogs; one lived 19 days, a second one 21 days, and a third was chloroformed when very weak after a survival of 70 days. Thorough autopsy demonstrated the completeness of this pancreatectomy. In the submucous layer of the intestine was found a nodule of pancreatic tissue, about 2 mm. in diameter, which on serial section showed only acinar tissue and no islands.

Blood sugar was not reduced by control injections of extract of spleen, liver, thymus and muscle, and only slightly by thyroid extract.

Mention is made of experiments by Best and Hepburn in which the pancreatic extract raised the respiratory quotient of totally depancreatized dogs from .68 — .74 to .85 — .94.

Banting, F. G., and Best, C. H., *Pancreatic Extracts*, J. Lab and Clin. Med., 8, 1922, 464-472.

The pancreas was taken from calves prior to the fifth month of fetal life and the extract was prepared by grinding up in Ringer's solution and filtering. Charts are given showing reduction of blood and urine sugar in totally depancreatized dogs following injections of such extracts. The results of these and other experiments are contained in the following conclusions:

"By intravenous and subcutaneous injections of neutral saline extracts prepared from the pancreas of the bovine fetus at about the

fifth month, the percentage of blood sugar and the daily urinary excretion of sugar are markedly reduced in depancreatized dogs.

"Daily injections of extract of pancreas enabled a depancreatized dog to live for seventy days.

"The active (antidiabetic) principle of such extracts is destroyed by boiling in strongly acid reaction but it is not affected by the presence of tricresol which may therefore be used as a preservative.

"The depressor action of the extract is short lived."

In addition the following observations concerning the preparation of extract from adult pancreas may be quoted:

"On December 8, 1921, Dog 35 (see Chart II) was completely depancreatized. The animal made a good post-operative recovery. On December 11 we injected 6 cc. of an extract prepared from the pancreas of this animal in the following way. The entire pancreas immediately after removal was cut into small pieces which were put into 0.2 per cent HCl in 95 per cent alcohol and allowed to stand till December 10. It was then macerated, filtered, and the clear filtrate evaporated to dryness in a warm air current. On December 11 this dry resin-like residue was emulsified in 25 cc. Ringer's solution and 6 cc. were given intravenously at 10 A. M. The blood sugar dropped from 0.46 to 0.18 in three hours.

"On December 12 at 3 P. M., 20 cc. of an extract made from the pancreas of a cow in the same manner as outlined above, was given on an empty stomach by stomach tube. The blood sugar fell from 0.41 at 3 P. M. to 0.28 at 7 P. M.. At 9 P. M., 10 cc. of this same extract was given intravenously. The blood sugar fell from 0.28 at 9 P. M. to 0.11 at 12 P. M. On December 13 (see Chart II), about 20 gm. each of liver, spleen, thyroid, and pancreas were extracted in identically the same manner as outlined above. There was no reduction in blood sugar following the intravenous injection of extracts of liver or spleen; a slight fall ocurred (from 0.35 to 0.27) following the administration of extract of thyroid and a marked one (from 0.27 to 0.13) following one of pancreas.

"On December 14 at 9:30, 10 cc. of extract of thymus made in the same way as were the liver, spleen and thyroid, were injected intravenously. There was a slight temporary fall froom 0.33 to 0.26 in one hour. At 2 P. M., 6 cc. of an extract prepared as above from pancreas and which had been placed in a parchment dialyzer in running water for twelve hours caused the percentage of blood sugar to fall from 0.33 to 0.09 per cent in three hours.

"On December 15, 200 mg. of the residue of ox pancreas extract were washed twice in toluol and then in 95 per cent alcohol, then dried again and emulsified in saline. At 10 A. M. this was given intravenously. The blood sugar dropped from 0.37 to 0.06 per cent in four hours. On December 16 at 9 A. M., 10 cc. of concentrated fetal calf extract were given per os. Blood sugar fell very slightly (0.38 to 0.35 per cent). On December 19, the animal, by this time considerably emaciated, was killed by chloroform."

Banting, F. G., Best C. H., Collip, J. B., Campbell, W. R. and Fletcher, A. A., Pancreatic extracts in the treatment of diabetes mellitus. *The Canadian Medical Association Journal*, 12, 1922, 141-146.

After a resume of the above experiments, the application of an extract of adult beef pancreas to the treatment of human diabetes is described.

"Up to the present time, February 22, 1922, the effects of these preparations have been observed in seven cases of diabetes mellitus and it is now evident that certain definite results can be obtained by their administration. The effects observed in depancreatized animals have been paralleled in man. The fall in blood sugar occurs and in two cases, repeatedly examined, a rise in the respiratory quotient, indicating carbohydrate utilization, occurs more or less coincidently with the attainment of a normal blood sugar level. Patients report a complete relief from the subjective symptoms of the disease. The sugar excretion shows marked decrease, or if dosage be adequate, disappears. Ketonuria is abolished, thus confirming a similar observation by Collip in diabetic animals (results as yet unpublished). These results taken together have been such as to leave no doubt that in these extracts we have a therapeutic measure of unquestionable value in the treatment of certain phases of the disease in man. In agreement with observations of other investigators on laboratory animals, it has been found that without careful control severe toxic reactions may be encountered and this will undoubtedly be a factor in the evaluation of the ultimate therapeutic utility of the method."

Patient No. 1 was a 14 year old boy with diabetes of about two years' duration, admitted to the Toronto General Hospital December 2, 1921.

"Jan. 4th. — Daily ration to consist of 50 gm. lean meat, 5 and 10% vegetables, and fruits and bran cakes to make up exactly 100 gm. of carbohydrates per day. Clear broth, cocoa, tea and coffee in moderation. Total intake about 450 calories.

"No further change in diet was made.

"This case was one of severe juvenile diabetes with ketosis. Previous to admission he had been starved without evident benefit. During the first month of his stay in hospital, careful dietetic regulation failed to influence the course of the disease and by January 11 his clinical condition made it evident that he was becoming definitely worse.

"The extracts given on January 11 were not as concentrated as those used at a later date, and, other than a slightly lowered sugar excretion and a 25% fall in the blood sugar level, no clinical benefit was evidenced.

"Daily injections of the extract were made from January 23rd to February 4th (excepting January 25 and 26). This resulted in immediate improvement. The excretion of sugar as shown in Chart I became much less. On days of treatment this varied from 7.5 to 45.1 gm., compared with a previous amount well over 100 gm. daily. The acetone bodies disappeared from the urine. The boy became brighter,

more active, looked better and said he felt stronger. No extract was given from February 5 to February 15. During this time sugar again appeared in the urine in large amounts, along with traces of acetone. Administration of extract in smaller doses after February 16 again resulted in lowered sugar excretion and disappearance of acetone from the urine. Chart II shows the fall in the total acetone bodies of the urine during the periods of treatment after January 23. Chart III gives a four hour record of the blood sugar following the administration of a single dose of 6 cc. extract on February 17. Chart IV shows the influence of extract on the amount of glucose excreted in each two hourly period when extract was being used. Table I records the volume of urine and amount of sugar excreted each day and blood sugar determinations. The qualitative test for the daily excretion of acetone bodies in the urine and the amount of extract given is also tabulated.

"Although the other six patients treated by these extracts were all favorably influenced by its administration, particular reference might be made to one — a severe case who had been excreting 20 gm. of glucose on a diet containing 10 gm. carbohydrate and 24 hundred calories per day. Following injection of the extract his urine became sugar free, and he obtained complete relief from severe depression and extreme lassitude. Respiratory quotients in this same case showed a definite rise after injection of the extract, confirming the increased utilization of carbohydrate.

"All patients were improved clinically. It is difficult to put in words what is meant by clinical improvement. Those who have been treating diabetes will have recognized as early signs of improvement a certain change in the skin, the appearance of the eyes, the behaviour of the patient, his mental and psychic activity, and the physical evidences, as well as his testimony, of increased vigor and desire to use his muscles."

Banting, F. G., Best, C. H., Collip, J. B., and Macleod, J. J. R., *Transactions of the Royal Society of Canada.* Third series, 1922. Vol. XVI, Section V. Preliminary Studies on the Physiological Effects of Insulin.

1. The Preparation of the Earlier Extracts (F. G. Banting and C. H. Best).

After mentioning the Ringer solution extracts of atrophic dog pancreas and of fetal calf pancreas and the later alcoholic extract of the latter, the authors describe a method of preparing the extract from adult beef pancreas. The first step consists in mincing the pancreas with addition of approximately an equal volume of 95% alcohol, acidified by addition of 0.2% hydrochloric acid. Fats can be removed by washing twice with toluene. The alcohol is removed by vacuum distillation at a low temperature. It is better to evaporate to one-fifth volume rather than to dryness. The aqueous extract thus obtained can be sterilized by Berkfeldt filtration. The results in a human

diabetic are said to have been found similar to those in the depancreatized dog, but sterile abcesses sometimes form owing to the presence of protein in the extract.

2. The preparation of the extract as used in the first clinical cases (J. B. Collip).

The best method for separating the active principle from protein, salts and lipoids was found to be the following: Equal volumes of fresh minced pancreas and 95% alcohol were allowed to stand for several hours with occasional shaking, and then filtered. To the filtrate was added 2 volumes of 95% alcohol. After allowing several hours for precipitation of most of the protein, filtration was repeated, and this filtrate was evaporated to small volume *in vacuo* at a temperature of 10 to 30 degrees C. An aqueous extract was thus obtained, which was washed twice with ether in a separatory funnel to remove lipoids, and then further distilled *in vacuo* to a pasty consistency. Addition of 80% alcohol and centrifugation then resulted in the formation of four layers, namely, a bottom layer of salt crystals, above it a saturated aqueous solution of salt, above this a flocculent layer of protein, and on top a clear layer of alcohol containing the entire active principle in solution. This top layer was pipetted off, and delivered into several volumes of 95% or (preferably) absolute alcohol. Several hours were then allowed for the active principle to precipitate out. It was then dissolved in distilled water, concentrated by vacuum distillation, filtered through porcelain, tested for sterility, and delivered to the clinic. Such extracts, practically free from proteins, salts and alcohol-soluble substances, could be made isotonic and injected subcutaneously without local reactions.

The Effect of Insulin on Normal Rabbits and on Rabbits rendered Hyperclycemic in Various Ways. Banting, F. G., Best, C. H., Collip, J. B., Macleod, J. J. R., and Noble, E. C.

1. The effect of Insulin on Normal Rabbits.

In over 150 normal rabbits fed on oats and sometimes also with sugar, the average sugar percentage in blood from the marginal ear vein by the Schaffer-Hartman method was 0.186 maximum, 0.095 minimum, 0.133 average. A physiological assay of insulin was based upon the definition that one unit is the amount of insulin which on subcutaneous injection lowers a rabbit's blood sugar by 50% in one to three hours. Relatively greater effects were obtained in depancreatized dogs. "Thus, 10 cc. of a certain extract injected into a rabbit reduced the blood sugar from 0.135 to 0.071 in 1½ hours, after which it began to rise again, whereas 20 cc. of the same extract given to a diabetic dog weighing about five times more than the rabbit caused the blood sugar to fall from 0.375 to 0.030 in 7 hours." The lowest blood sugar found in rabbits was 0.01 per cent 2¾ hours after injection of insulin. The purest preparations gave the quickest fall in blood sugar.

Sufficiently large doses of insulin caused hyperexcitability, followed by coma and rapid or periodic breathing, with sluggish conjunctival

reflexes, widely dilated pupils and normal rectal temperature. Slight stimuli, even shaking of the floor, gave rise to violent convulsions in the form of tumbling or running movements, lasting one or two minutes. In the absence of outside stimuli, the interval between such convulsions was generally about fifteen minutes. Death finally resulted from respiratory failure.

"Out of a total of 123 rabbits receiving insulin, convulsions were observed in 26 cases, and the maximum percentage of blood sugar at which they ocurred was 0.047 (except in one animal in which 0.067 was found), and the minimum percentage at which there were no convulsions was 0.037." By comparison with the observations of F. C. Mann (*Proc. Amer. Physiol. Soc.*, Dec., 1920) on dogs made hypoglycemic by removal of the liver, the above symptoms were attributed to the low blood sugar, and this assumption was supported by the observation that injection of sufficient quantities of glucose (4 gm. in 20% solution subcutaneously) restored the animals to normal. Rarely recovery was possible without injections. Injections of pentoses or of salt solution had no effect.

2. The Effect of Insulin on Hyperglycemic Animals.

Rabbits fed on oats and sugar were made hyperglycemic by various methods (asphyxia, carbon monoxide poisoning, epinephrine, piqûre, and ether). Portions of liver were removed after death for glycogen analyses. A table is given showing that hyperglycemia was nearly or completely prevented by insulin injections in every experiment, and frequently hypoglycemia was produced.

Banting, F. G., Best, C. H., Collip, J. B., Hepburn, J., and Macleod, J. J. R. The effect produced on the respiratory quotient by injections of insulin.

The subject of the first experiment described was a physician, aged 29 years, with diabetes of 6 years duration. On a diet containing 10 gm. carbohydrate and 1200 calories the urinary sugar was 15 to 30 gm. daily during several months, the blood sugar 0.28 to 0.33%, acetonuria was continuous, and the respiratory quotient on February 17, 1922, was 0.74 in several observations during two hours. 4 cc. insulin was then injected subcutaneously and 20 gm. cane sugar given by mouth, and the respiratory quotient within 2 hours rose to 0.90. In another experiment with 2 cc. of insulin the quotient rose to 0.82 in 3 hours. Similar results are said to have been obtained by Dr. W. R. Campbell on two other patients.

Experiments are next described on four totally depancreatized dogs in which injections of 10 cc. insulin or less, together with feeding of 20 to 30 gm. cane sugar, caused the respiratory quotient to rise from the usual low level of about 0.64 to levels between 0.85 and 0.93 or in one instance to 1.06. With the exception of an early experiment in one dog, the sugar alone had no important effect upon the quotient.

The injection of insulin alone raised the quotient from 0.65 only to 0.70, but with the subsequent feeding of 20 gm. cane sugar it rose to 0.89.

A normal dog starved for three days was given 4 cc. of insulin subcutaneously with the result that the respiratory quotient rose from 0.77 and 0.75 to 0.90 (in 42 minutes after injection) and then fell to 0.85 (in 1 hour 6 minutes) and 0.78 (in 1 hour 36 minutes).

Banting, F. G., Best, C. H. Collip, J. B., Macleod, J. J. R., and Noble, E. C. The Effect of Insulin on the Percentage Amounts of Fat and Glycogen in the Liver and Other Organs of Diabetic Animals.

In three totally depancreatized dogs treated with insulin injections and sugar feeding, the liver glycogen was found to be respectively 4%, 12.58%, and 13.27%, in contrast to the usual low percentages in untreated animals.

In four depancreatized dogs receiving insulin injections and sugar feeding, the heart glycogen was found to be 0.725%, 0.600%, 0.570% and 0.296%. From comparison with untreated diabetic dogs, it is concluded that insulin tends to reduce the abnormally high heart glycogen of diabetic animals to within normal limits.

The figures obtained for glycogen in the skeletal muscles were insufficient to warrant a conclusion.

The total fatty acid content of the liver was found to be reduced in diabetic dogs receiving insulin and sugar as compared with untreated controls. (12.25, 14.10, and 9.90% in untreated diabetic animals, 7.425, 2.19, and 4.41% in those treated).

Total fatty acids in the heart showed little definite change (4.26 and 2.59 in untreated, 3.09 and 2.08% in treated diabetic animals).

The total fatty acids in the blood were reduced by the treatment of depancreatized animals with insulin injections and sugar feeding (1.21 and 1.12% in untreated, 0.333, 0.270 and 0.531% in treated animals).

"The observations taken as a whole show that insulin given to sugar-fed diabetic animals causes the fat to become reduced in the liver at the same time as glycogen accumulates. Whether glycogen would also accumulate in this organ without ingestion of sugar, we cannot at present say. It is clear that there must be a stage following the administration of insulin when glycogen and fat both are present in considerable percentage in the liver. This is shown in experiment 56."

Banting F. G., Best, C. H., Collip, J. B., Macleod, J. J. R. The Effect of Insulin on the Excretion of Ketone Bodies by the Diabetic Dog.

Three experiments showed that the usual slight acetonuria of totally depancreatized dogs (maximum daily excretion 0.210, 0.187, and 3.141 gm. of total acetone respectively in the 3 dogs) was completely abolished by insulin injections.

Macleod, J. J. R., *Pancreatic extract and diabetes*, Canadian Medical Association Journal, 12, 1922, 423-425.

After mentioning the experimental preparation of extract and the difficulties encountered in passing to large-scale production, the author continues:

"Briefly, the most significant of the results which have been obtained are as follows: Subcutaneous injection of the extract into normal rabbits causes the percentage of sugar in the blood to fall, and when this reaches a certain level (about 0.045 per cent.), perfectly characteristic symptoms of a convulsive character appear and, if left alone, the animal passes into a comatose condition, which soon ends in death. If a solution of sugar be injected subcutaneously when the symptoms appear, the animal immediately recovers and may remain perfectly normal or pass again into the convulsions, which may be removed a second time by injections of sugar. Many observations have convinced us that these symptoms are definitely related to the lowering of blood sugar—they may indeed be called hypoglycaemic convulsions—and this is all the more interesting in light of the work of F. C. Mann, who found similar symptoms to develop in dogs when the blood sugar was lowered to about 0.04 per cent by isolation of the liver from the circulation. The discovery of this effect on normal rabbits has proved a most important one in connection with the isolation and purification of the extract, since it affords a readily available laboratory test object. It obviates the necessity of using depancreated dogs for testing the potency of the extract and therefore has greatly facilitated our work. As is to be expected, an extract which acts only feebly on normal rabbits has a much more pronounced effect on the hyperglycaemia of diabetic dogs.

"Not only is the blood sugar lowered in rabbits that are normal but also in those rendered diabetic by any of the experimental methods usually employed to bring this about. These are puncture of the floor of the fourth ventricle (piqûre), asphyxia, poisoning by carbon monoxide gas, ether, or adrenalin. None of these causes hyperglycaemia in rabbits after injecting then with sufficient amounts of pancreatic extract. There may occasionally be a slight increase in the percentage of blood sugar but never to anything like the extent usually observed without extract. The animals used for these experiments were always well fed with carbohydrates and the glycogen content of the liver determined. The importance of this result is that it shows us that even the purely experimental forms of diabetes have much in common with the clinical forms."

The results of glycogen and fat analyses are discussed as follows:

"The importance of these observations rests on the fact that they show that the function which is primarily regulated or controlled by the internal secretion of the pancreas is that concerned with the deposition of glycogen. They would seem to suggest that glycogen must be an essential preliminary stage in the utilization of sugar by the animal body and that when the pancreatic hormone is absent excess of sugar leads to the mobilization of large quantities of fat."

After mentioning the observations of elevation of the respiratory quotient the author concludes:

"In the light of these various types of evidence we feel justified in expressing the belief that it will be possible by administracion of pancreatic extract, to treat diabetes in man much more satisfactorily than has hitherto been the case. Dietetic control must no doubt remain an important feature of treatment, and will probably be all that is neccesary in the earlier stages of the disease, but in the later stages it is hoped that administration of extract will prove of value. What other therapeutic uses the pancreatic extract may have remains as yet undetermined".

Banting, F. G., Best C. H .,and Macleod J. J. R., *The internal secretion of the pancreas. Proc. Amer. Physiol. Soc.,* Dec. 1921. Am. J. Physiol., 59, 1922, 479.

This report merely summarizes briefly the findings described in the first and second papers reviewed above. (Banting, F. G. and Best, C. H., *Communication to the Academy of Medicine* (Toronto) February 7, 1922, and Banting F. G., and Best, C. H. The internal secretion of the pancreas, *J. Lab. and Clin. Med.*, 7, 1922, 251-256).

Banting, F. G., Best, C. H., Coltip, J. B., Macleod, J. J. R., and Noble, E. C., *Amer. J. Physiol.*, 62, 1922, 162-176. The Effect of Pancreatic Extract (Insulin) on Normal Rabbits.

The rate of action of subcutaneous doses of insulin varies; it is decidedly slower in impure preparations than in those giving only faint protein reactions. With the former, the blood sugar may not in four hours have reached its minimum; with the latter, the minimum may be reached before four hours. If the sugar is not below 0.065 in four hours another sample should be taken in five or six hours. If it does not fall below this level, experience justifies arbitrarily designating the quantity as half a rabbit dose.

When all rabbits are fed on oats and hay for the sake of uniformity, the results of the same dose of the same preparation are not identical in different rabbits, as respects both blood sugar and symptoms (table gives examples).

Other findings are covered by the following conclusions:

"1. Purified alcoholic extracts of pancreas, for which we suggest the name *insulin,* when injected subcutaneously into normal rabbits cause the percentage of sugar in the blood to fall within a few hours.

"2. As a tentative basis for the physiological assay of insulin, we consider one unit the number of cubic centimeters which causes the blood sugar of normal rabbits to fall to 0.045% within four hours. This dose is decidedly active in lowering the blood sugar in diabetic patients.

"3. As the blood sugar falls, as the result of insulin injections, the rabbit exhibits highly characteristic symptoms, earliest of which are signs of hunger and thirst, hyperexcitability and apparent fear.

"4. The animal may recover from these earlier symptoms, but

frequently, with active preparations, the hyperexcitability becomes extreme and clonic convulsive seizures involving the entire body and lasting for several minutes supervene. Between the convulsive seizures the animal is lying on its side in a more or less comatose condition with shallow, rapid and frequently periodic breathing.

"5. In the great majority of cases exhibiting convulsions the blood sugar has been found to be about 0.045%.

"6. Subcutaneous injections of dextrose solutions antidote the convulsions and other symptoms, so that the animal in a few minutes becomes restored to a tolerably normal condition. Similar symptoms may again develop but they also can be antidoted by dextrose.

"7. In animals that die as a result of the symptoms, a peculiar muciginous degeneration of the subcutaneous tissues of the abdominal wall is very commonly observed."

Earlier in the article, it is stated: "Sometimes this material forms a more or less circumscribed tumor and, particularly after sugar injection, a considerable amount of fluid may be present along with the mucin-like material. The fluid has strong reducing properties. Nowhere else in the body have we observed this peculiar change. It is not due to any local action of the insulin, since this is always injected in the back."

Hepburn, J. and Latchford, J. K., *Amer. J. Physiol.*, 62, 1922, 177-184. Effects of Insulin (Pancreatic Extract) on the Sugar Consumption of the Isolated Surviving Rabbit Heart.

Mention is made of unpublished work showing that insulin does not influence the glycolytic power of blood *in vitro* or the rate of post-mortem glycogenolysis in the liver. The hypoglycemic influence, therefore, apparently resides in the active tissues.

Reference is made to conflicting results of Maclean and Smedley, Knowlton and Starling, and Patterson and Starling, and particularly to A. H. Clarke's observation that the pancreas itself does not consume sugar appreciably, but very decidedly increases consumption by the heart when the perfusion fluid is first passed through it.

Rabbit hearts were perfused with Locke's fluid, containing 0.2% glucose. The perfusate was not only analyzed for sugar by the Shaffer-Hartmann method, but in two cases also hydrolyzed at the end of the experiment and the sugar content found not increased.

The entire quantity of insulin was sometimes added to the perfusion fluid, either at the beginning or later, but the best method was to add 0.1 to 0.25 cc. of insulin every 15 minutes. The pH was thus kept at 7.2, instead of increasing as it otherwise tended to do. Bacterial contamination was excluded.

Conclusions:

"The average sugar consumption of the isolated rabbit heart perfused with Locke's solution was found to be 0.87 mg. per gram per

hour. When insulin of proved potency, as tested by its ability to lower the blood sugar in normal rabbits, was added to perfusion fluid, the average sugar consumption rose to 3.06 mg. per gram per hour.

"The average glycogen content of the treated and untreated hearts was practically the same."

F. M. A.

THE ISLANDS OF LANGERHANS IN ELASMOBRANCH AND TELEOSTEAN FISHES.

Part I. The Islands of Langerhans in the Skate.

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From many points of view, theoretical and practical, the islands of Langerhans in fishes are of especial interest and importance, and for the following reasons:

In Elasmobranchii (cartilaginous fishes) the islands, as will be seen, are large and numerous, and retain, to a great degree, their primitive relationship to the ducts, thus affording a relatively large amount of island tissue for experimental work, and presenting many points of phylogenetic and ontogenetic interest.

In Teleostei (bony fishes) their chief interest lies in the fact that in these forms there occur what have been described as "principal islets" — isolated and generally encapsulated structures quite distinct from the main mass of the pancreatic tissue. It is of the utmost importance that the real nature of these bodies be determined, for, while it has long been assumed that they are structurally identical with the island tissue embedded in the substance of the pancreas in these fishes and in Vertebrata generally, their minute structure has never been adequately described and figured from the standpoint of modern cytology. If, as alleged, these "principal islets" consist entirely of island tissue, they will afford material for the experimental demonstration of the functional significance of the islands of Langerhans, and of the correctness of the interpretation of these as an endocrine tissue, the primary function of which is the regulation of carbohydrate metabolism.

For these reasons, then, and in view of the striking and important results obtained by Prof. J. J. R. Macleod with material obtained from both these sources (*vide* this issue, p. 119)

it has been thought well to present a resumé of the more important histological results so far obtained from a series of observations now in progress on these two groups of fishes. It is proposed to present these results in outline as follows:— a consideration of the islands in Elasmobranchii as illustrated by

I. The Skate (*Raja* spp.) and
II. The Dogfish (*Squalus acanthias*), and a description of
III. The "Principal Islets" in Teleostei.

I. The Islands of Langerhans in the Skate.

Macroscopically the pancreas in the skate, as in Elasmobranchii generally, is a large compact organ, consisting of a large dorsal and a smaller ventral lobe, thus differing from the pancreas in Teleostei, in which it is, as a rule, extremely diffuse.

On section the appearance presented offers a marked contrast to that seen in other Vertebrata. The most striking feature is the occurrence of large, lightly-staining areas — the "helle Felder" of Oppel[1]. These light fields are irregular in size, shape and distribution, and are sharply demarcated from the surrounding zymogenous tissue. On examination it is found that these areas apparently consist of masses of island tissue together with the epithelium of the ducts around which they are grouped. (Fig. 1).

The Ducts. In sections through the skate pancreas the ducts may be seen cut across in various directions, and to be, in most instances, surrounded by, or associated with, island tissue. (Figs. 1 and 2). The smaller ducts, as described by Oppel (*loc. cit.*) are, in the skate, numerous and richly branched, and are lined, as described by him and by Diamare[2], with a double epithelium. This condition is also noted by Vincent and Thompson[3] in the skate and other Elasmobranchii. The cells of the inner layer are small, with indistinct cell boundaries. Those of the outer layer, on the other hand, are large and distinct, and bear a striking resemblance, as seen in ordinary preparations, to the islet cells immediately surrounding them.

A fact of great interest is that among the cells forming the outer layer occasional cells may be seen, which, even with

ordinary stains, (e.g. Heidenhain's iron hæmatoxylin) present a different appearance from the rest. This was remarked by Oppel and other observers, and also by Vincent and Thompson in various species. The probable nature and significance of these cells will later be referred to.

The Islands. The unusual amount and peculiar distribution of the island tissue in Elasmobranchii is in part responsible for the earlier denial of its existence in these fishes, and for the scant attention it has since received. Diamare (*loc. cit.*) in 1899 denied the existence of islands. Oppel, in 1900, while calling attention to these structures in the skate and other species, and pointing out their similarity to the true islands in other forms, refers to them and actually figures one under the name "pseudo-intertubulären Zellenhaufen." In the same year, however, Gianelli[4] came to the conclusion that they were true islands, and the subsequent investigations of Laguesse[5] and Helley[6] seem to have established, as might have been anticipated, the correctness of Gianelli's conclusion. Some uncertainty, however, still prevailed, since Rennie[7], writing in 1904, remarks "The fact is not without interest that hitherto observers have failed to find anything like epithelial blood-islets within the pancreas of elasmobranchs."

The true nature of these structures appears, however, to have been recognized by Vincent and Thompson, who state that "The appearance of the light or clear areas in the pancreas of elasmobranchs is certainly at first sight very different from that of the islets of Langerhans in any other group of vertebrates, and it is not surprising that Diamare was at first unwilling to admit their homology with the mammalian islets. But from a study of Diamare's own drawings and the observations of Laguesse and ourselves, it seems clear that the groups of lightly stained cells arranged here and there round the smaller ducts of the elasmobranch pancreas do as a matter of fact, represent the primitive type of islet structure in vertebrates." (*loc. cit.* p. 279).

The reason of this tardy recognition lay in the fact that, until the year 1907, conclusions rested upon very uncertain ground, and the absence of any concise conception and adequate definition of an "island" resulted in the separation of observers into two chief groups (1) those who regard the islands as structures *sui generis*, and (2) those who look upon

them as temporarily ehausted acini, capable, after a period of rest, of retransformation into acinar tissue. This difference of opinion, as above indicated, has arisen through the absence of definite criteria by which island cells may be distinguished and differentiated from associated cells.

As Bensley[8] notes as late as 1911 "the prevailing definition of an islet cell is by means of negative characters. Thus an islet cell is defined, not by what it has, but by what it has not."

Positive data had, however, been adduced in 1907 by Lane[6], which afford definite criteria by which island cells may be defined. Lane established, by microchemical methods, the fact that the islands of Langerhans are made up of two distinct types of cell, which he termed the *alpha* and *beta* cells respectively. Lane's paper, while published in the same year as that of Vincent and Thompson, was probably of later appearance, and Lane's results were therefore not available to them. It is for this reason, and owing to the lack of employment of adequate technical methods, that the work of Vincent and Thompson, while constituting the most important recent contribution to the subject, cannot be regarded as fulfilling modern cytological requirements.

The investigations of the writer, who has employed the methods of Lane as originated by him, and with modifications, have yielded results which appear to establish the morphological identity of the islands of Langerhans in the Elasmobranch pancreas with those of other Vertebrata.

As before indicated, and as will be seen in figures 1 and 2, the island tissue is chiefly distributed in intimate relation to the ducts. Some of the smaller islands, however, appear to be isolated (figs. 1 and 3). In some instances the island cells appear to be directly continuous with the outer layer of the duct epithelium, in others they are seen to be separated from them by a distinct layer of connective tissue (fig. 2).

The smaller isolated islets are sharply demarcated from the surrounding zymogenous acini and in no instance appear to be confluent with them.

Both large and small islands are seen to consist entirely (apart from connective and vascular elements) of two types of cell, differing in size, shape, relative number and chromatin content. The most apparent difference, however, lies in their

respective reaction toward Bensley's neutral gentian, as employed after the method of Lane, viz., after fixation with alcohol and aqueous chrom-sublimate respectively. With the former fixative the cytoplasma of the larger cells (*alpha* cells of Lane) is seen to be filled with minute, deeply-staining granules, while the smaller and more numerous (*beta* cells of Lane) appear clear. With aqueous chrom-sublimate, on the other hand, the *beta* cells exhibit granules, whilst the *alpha* cells remain clear.

The result of the application of Lane's method to the Elasmobranch islet is in accord with his own result for the mammalian islet, and is well seen in fig 3, which represents a section through a small isolated islet, measuring 32 by 56 micra.

Its independence of the zymogenous tissue is emphasized by a slight shrinkage. It contains some five *alpha* cells averaging 12 by 15 micra, in which the granules, much smaller than the zymogen granules, are characteristically stained. It is probable that the peripheral position of the *alpha* cells with their small granules, lying as they do adjacent to the zymogenous tissues in instances such as this, may give rise to the assumption, insisted upon by Vincent and Thompson, that cells transitional between islet and acinar cells are of frequent occurrence. This is also remarked by Bensley, who says (*loc. cit.* pp. 376-7) "I fear that the idea, that *alpha* cells are transitions, is merely a hasty assumption based on the fact that these cells sometimes occur on the surface of the islet and sometimes are interposed between the acinus cells and the islet cells." This misleading interpretation would be all the more probable in sections stained with hæmatoxylin, as most of Vincent and Thompson's appear to have been.

With one exception no other cells exhibit the characteristic reaction with Lane's reagents. This exception lies in the large cells of the outer layer of duct epithelium. As before indicated, certain of these cells have long been known to exhibit peculiarities in staining reaction, and, as pointed out by Oppel (*loc. cit.*) to contain "fuchsinophile Körnchen". The cells, in appearance and in staining reaction with neutral gentian, are identical with the *alpha* cells of the islets (cf. figs. 3 and 1), and may thus justly be called "Langerhans' cells" — a term applied by Helley to the entire outer layer. This is of interest

in view of the embryological derivation of the islets from the duct epithelium, as established by Helly, Pearce[10], and others, and the fact that Weichselbaum and Kyrle[11], as pointed out by Bensley (*loc. cit.* p. 341), "record experimental observations which indicate that the duct epithelium possesses the power of forming islets even in adult life."

While the histological and cytological evidence reveal an intimate association between island and duct, no indication of the occurrence of "transitional cells" and therefore of the conversion of acinar into island tissue, is to be found.

These "transitional cells" as well as the "bathychrome tissue" of Vincent and Thompson are, it is submitted, interpretations made possible through the employment of a technique which fails to afford definite means of cytological differentiation, and a consideration of these is reserved for a later paper.

Summary and conclusions. An examination of the pancreas and islands of Langerhans in various species of skate indicates that:

1. The islands are strictly homologous with corresponding structures in other groups of Vertebrata, and consist essentially of the *alpha* and *beta* cells of Lane.

2. Their distribution and intimate relation to the ducts is not to be regarded as constituting a fundamental difference as compared with conditions in other groups (e.g. mammals) but as a more primitive condition, of phylogenetic and ontogenetic interest.

3. Their apparent complete independence of the acinar tissue, and the absence of any indication of "transitional cells" are opposed to the theory of transformation of acinar into island tissue and *vice versa.*

Atlantic Biological Station, St. Andrews, New Brunswick
September 12, 1922.

Explanation of the figures

Fig. 1. Section of pancreas of Skate (*Raja erinacea*) 5 micra, iron hæmatoxlin and congo red. X 70. The clear areas show ducts cut in various planes and the surrounding island tissue. Several isolated islets are also shown.

Fig. 2. Section through small ducts and islands from the same preparations as fig. 1. X 320. The continuity of the outer

layer of the two-layered epithelium with island tissue is to be seen at the point of contact of the two ducts. Above the left hand duct is a small isolated and encapsulated islet.

Fig. 3. Section of a small islet (32 x 56 micra) with surrounding zymogenous acini. Section 5 micra thick; stained with Bensley's neutral gentian. X 650. Three *alpha* cells with their nuclei are seen to the right and below, and two to the left. These are distinguished from the remaining *beta* cells by the granules in the cytoplasm, which, as will be seen, are much smaller than the zymogen granules in the surrounding acini. Note also the independence of the islet from these acini.

Fig. 4. Section of small duct from the same preparation as fig. 3. X 650. In the outer layer of the duct epithelium below are to be seen three or four cells identical with the *alpha* cells seen in fig. 3. To the right is a small group of islet cells in close relation to the outer layer of duct epithelium.

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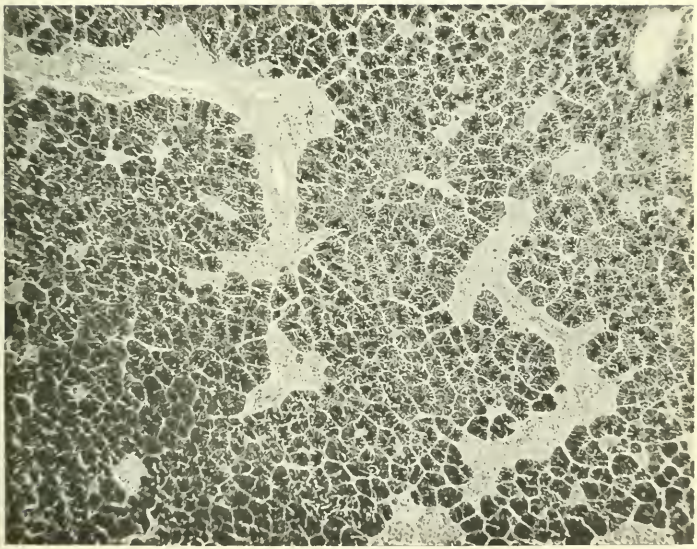


Fig. 1.

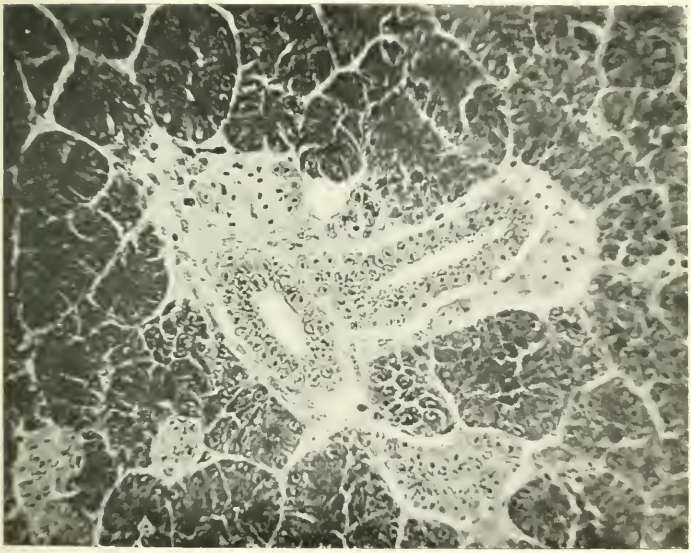


Fig. 2.

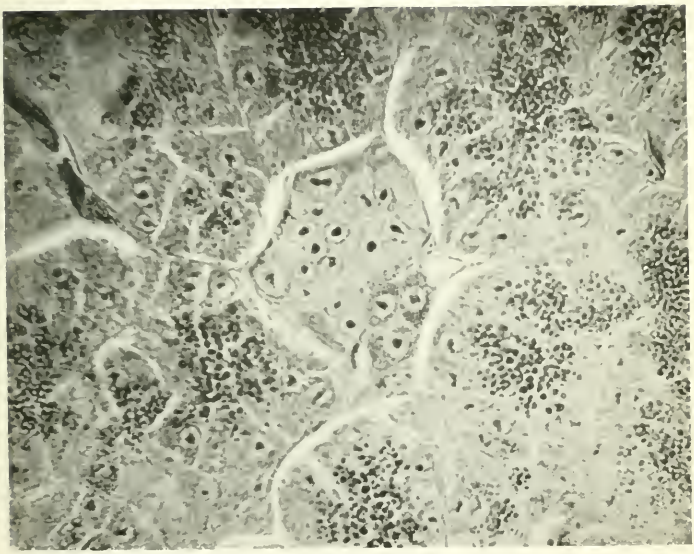


Fig. 3.

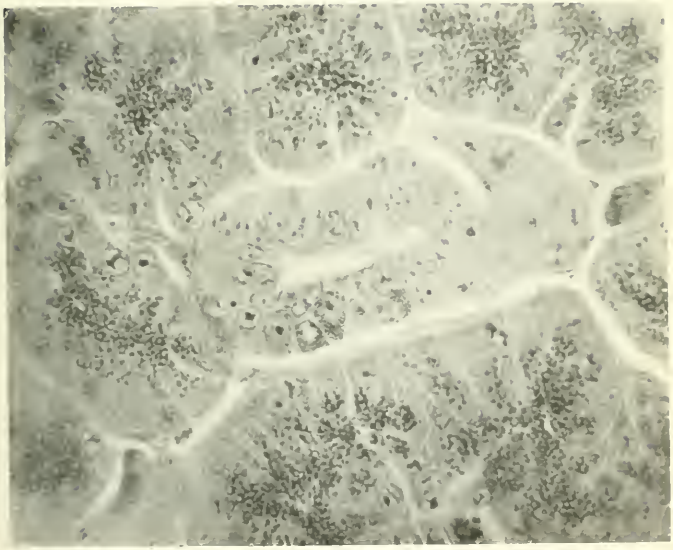


FIG. 1.

THE SOURCE OF INSULIN.

A STUDY OF THE EFFECT PRODUCED ON BLOOD SUGAR BY EXTRACTS OF THE PANCREAS AND PRINCIPAL ISLETS OF FISHES.

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The hypothesis that it is to an internal secretion of the islets of Langerhans that the pancreas owes its well-known relationship to carbohydrate metabolism is not supported by any proof of a direct nature. The frequent occurrence of pathological changes in the cells of the islets in diabetes, the fact that experimental ligation of the pancreatic ducts is not followed by diabetes although it causes the zymogenous cells to degenerate to a much greater extent than the insular, and the recent discovery in the writer's laboratory by Banting and Best[2] that extracts of degenerated pancreas have the power to lower the blood sugar in diabetic animals, furnish the main indirect evidence in support of the hypothesis. The anatomical evidence is conflicting. Laguesse[3], H. H. Dale[4] and Swale Vincent and Thompson[5], without denying the possibility that the islets may furnish an internal secretion, have maintained that the islet cells are closely related to the zymogenous, that anatomical continuity can often be seen between them and that under certain conditions transition forms of cells are common in the pancreas throughout the vertebrates. R. R. Bensley[1], however, taking advantage of the more modern microchemical methods of staining, particularly the method of Lane[6], showed that the authors referred to had not properly distinguished between islet and zymogenous cells and that when this is done, by the demonstration in the former of Lane's *alpha* and *beta* granules, no transformation of the one kind of cell into the other can be demonstrated under the conditions described by Dale and by Vincent and Thompson.

NOTE: The expenses of this investigation were in part defrayed by a grant from the Carnegie Corporation.

Bensley's view is very strongly supported by the important work of Rennie[7] who discovered that the islet tissue in the bony fishes (Teleostei) is collected into nodules which are often encapsulated and are thereby separated from the zymogenous tissue. The latter, in these fishes, occurs as narrow bands spread out in the mesentery most abundantly along the branches of the portal vein, and near the pyloric caeca. Inasmuch as Rennie's work was done before the introduction of the more modern methods of microchemical staining, there is at present, however, no irrefutable evidence that the cells of the principal islets which he discovered are really homologous with those of the islets of Langerhans in the mammalian pancreas.

In connection with the present investigation and in relationship to Rennie's discoveries it is important also to note that in the cartilaginous fishes (Elasmobranchi) the islets and the zymogenous tissues have the same general relationships as in the higher vertebrates, the former being scattered in the compact pancreas which is situated near the duodenum. Swale Vincent and Thompson have found that the islet tissue in these fishes is in intimate relation with the duct epithelium[4].

It is evident that if Rennie's suposition is correct that the principal islets of Heleostei are composed of the same cells as those of the islet tissue of the pancreas of the higher vertebrates, and if an internal secretion regulating carbohydrate metabolism is derived from these islets, then it should be possible to prepare from the principal islets an extract having a potent influence on the symptoms of diabetes.

Rennie, working with T. Fraser, attempted to demonstrate this. These workers observed the symptoms of several diabetic patients to whom the glands were given by mouth, often in considerable amounts, either in a raw state or as extracts, and, in one case, by subcutaneous injection of a saline emulsion. The results were subsequently shown to be too unreliable to prove any beneficial action of the treatment. Inadequate control of diet, the severity of the cases chosen, the exhibition of the gland substance by mouth all militated against the success of the investigation. In the one case in which an unheated saline extract of the principal islet of "Lophius" was given it is reported that "the amount of reaction caused by the injection, accompanied as it was with no

improvement caused us to abandon this method of treatment." In light of the results of the present investigation it is unfortunate that more carefully prepared extracts were not used subcutaneously.

As a result of the improved histological technique introduced by Lane and Bensley (loc. cit.) and of the recent demonstration by Banting, Best, Collip, Macleod and Noble[9] that an alcoholic extract of mammalian pancreas—known as insulin—profundly lowers the percentage of blood-sugar in normal rabbits, the whole question as to the significance of the islet tissue, and particularly whether it is the source of insulin, is reopened for investigation.

There are two aspects to the problem, the one being to compare by modern histological methods the exact cytological structure of the islets in mammalian and Elasmobranch pancreas with that of the principal islets found by Rennie in the Teleostei, and the other, to study the effect of extracts prepared from these sources on the percentage of blood sugar in normal rabbits . The former of these problems has been undertaken by Dr. Slater Jackson of McGill University and a preliminary report of his work appears in this Journal, whilst the latter forms the material of this paper.

In general, the plan of investigation has been to observe from time to time the amount of blood sugar in normal rabbits injected with extracts prepared from the following sources:— (1) the pancreas of representative Elasmobranchs [Squalus (dog fish) and Raja (skate)]; (2) the principal islets of representative Teleostei [Myoxycephalus (sculpin) and Lophius (angler fish)] and (3) the zymogenous (acinar) pancreatic tissue, as free as possible from islets, in the same and certain other Teleostei.

Methods.

Preparation of extracts. In practically every case the gland was cut up in small pieces and placed in alcohol of about 60 percent., made faintly acid with hydrochloric acid. When the amount of tissue was considerable, stronger alcohol (95 percent.) was used. The collected material was usually left standing in a refrigerator* at — 15°C. for several days. To prepare

* Throughout the paper when 'refrigerator' is mentioned this is the one referred to.

the extract the tissue was removed from the alcohol and thoroughly ground in a mortar with sand, the alcohol being then gradually added with constant rubbing, so as to ensure thorough extraction, after which the extract was pressed out through several layers of gauze and the residue extracted a second time. The crude extracts were filtered through paper and the clear filtrate placed in large porcelain developing trays which were then placed in a drier consisting of an oblong box (4 x 1 x 1 feet) open at the narrow ends and through which a rapid current of warmed air was passed by means of a fan. The rapid movement of the warmed air over the thin layer of fluid in the trays causes rapid evaporation so that the temperature of the fluid does not rise above 30°C. (and is usually much less) until evaporation is nearly complete. When the volume in each tray was reduced to about 10cc. the contents were filtered into a small bottle which was kept in the refrigerator (and the contents frozen) until used for injection.

In several cases the procedure described elsewhere[10] for the preparation of insulin from the ox pancreas was employed, but since, with the relatively small quantities of tissue used, it was not found that much precipitate could be obtained by bringing the percentage of alcohol to ninety (after previous precipitation of the proteins) this method was abandoned. In other cases, particularly when large amounts of pancreas of dog fish or skate were used, the extract after evaporation contained much fat which was removed by shaking with ether. Since the work was in the main qualitative, rather than quantitative in nature, it was not as a rule attempted to regulate the volume of the final solution so that it bore a relationship to the amount of gland extracted. However, a few observations of this character were made.

To study the action of the extracts, from 2 to 15cc. was injected under the skin of the back in well-fed rabbits from which 1cc. of blood had just been removed from the ear vein. Further samples of blood were subsequently removed at regular intervals and the percentage of sugar in each determined by the Shaffer-Hartman method after precipitation of proteins by sodium tungstate and sulphuric acid (Folin's reagent).

Results.

Elasmobranch Pancreas. In both the dog fish (Squalus Acanthias) and the skate (Raja) this gland is compact and readily seen on opening the body cavity. It is more or less attached at its broad end to the first portion of the intestine, the narrow end extending towards the spleen. In a small skate weighing about 1 kg. the pancreas weighed 3 gm., i.e. about 0.3 per cent. of the body weight, and in a large "barndoor" skate weighing 16.4 kg. it weighed 31.5 gm. (about 0.2 per cent. of the body weight).

Raja.

Experiment I. The pancreas from five skate each weighing about 1—1.5 kg., after being kept in approximately 50 per cent. alcohol at about —15°C. for one week, were extracted by the usual method and the filtrate was evaporated to 9 cc. in warm air. All of this was injected into an albino rabbit (2.3 kg., female) suffering from respiratory trouble which was afterwards found to be due to tubercular tumours in the lungs.

July 14 —	10.30 a.m.	0.096 0.093	percent blood sugar.
	10.30 - 11.00 a.m.		Injection of extract. Owing to breaking of hypodermic needle the injection was delayed.
	12.00 noon	0.046 0.050	percent blood sugar.
	1.20 p.m.	0.056	" " "
	2.40 p.m.	0.058	" " "
	4.10 p.m.	0.066	" " "
	6.30 p.m.	0.094	" " "
July 15 —	10.00 a.m.	0.108 0.108	" " " " " "
"	"	"	

Although the reduction in blood sugar was marked it did not reach the level (of 0.045) at which the symptoms described elsewhere make their appearance. It attained its lowest level about from three to four hours after the injection.

Experiment II. The pancreases were removed from 6 small skate and placed in 50 per cent. alcohol, in which they remained part of the time at room temperature and part in the refrigerator for four days, when an extract was prepared as in experiment I and injected into a rabbit (wt. unrecorded).

July 17 — 12.00 noon — 0.120 percent blood sugar.
12.15 p.m. — Injected 4-5 c.c. of extract.
2.00 " — 0.079 percent blood sugar.
2.15 " — Further injection of 4-5 c.c. of extract.
3.45 " — 0.075 percent blood sugar.
5.35 " — 0.064 " " "
9.15 " — 0.082 " " "
July 18 — 4.30 " — 0.125 " " "

This observation was not so well controlled as the previous one but it shows much the same results. The blood sugar reached its lowest point of 0.064 per cent. in about 3½ hours after the second injection but was still decidedly subnormal after seven hours. The animal showed no symptoms.

No attempt was made in these two experiments to remove all of the protein from the extracts. In those following, this was done by raising the concentration of alcohol to between 70 and 80.

Experiment III. The pancreases of several small skate that had been kept in 50 per cent. alcohol in refrigerator over night were extracted in a mortar with sand and filtered. The residue was extracted with fresh 50 per cent. alcohol a second time and to the combined filtrates sufficient alcohol (95 per cent.) was added so as to give about 70 per cent. alcohol in the mixture, when only a slight precipitate formed. The solution was then evaporated in an air current to 4 cc. (cool air used most of the time so that 5 hours occupied in evaporation). Alcohol was then added so as to give about 85 per cent. in the mixture, when a considerable precipitate separated. This was centrifuged, the *supernatant fluid* evaporated and the residue injected into a rabbit (brown) weighing 2.7 kg., with the following results.

July 21 — 12.00 noon — 0.093 percent blood sugar.
12.05 - 12.30 p.m. — Injection slowly of 15 c.c. extract.
1.40 p.m. — 0.041 percent blood sugar.
3.15 " — 0.044 " " "

A marked hypoglycæmic effect is evident in 1¼ hours after the injection and it persists for at least 3 hours. It is interesting that no symptoms were observed although the blood sugar fell to below the level at which these usually occur (cf. 10).

The precipitate was washed with absolute alcohol by cen-

trifuging and then suspended in 10 cc. water and injected into the same (albino) rabbit used in Experiment I.

July 21 — 11.30 a.m. — 0.110 percent blood sugar.
11.35 " — Injection.
1.25 p.m. — 0.070 percent blood sugar.
3.05 " — 0.063 " " "

Evidently the percentage of alcohol was such as to only partially precipitate the insulin.

Experiment IV. In order to obtain stronger extract the pancreases removed on different days from 43 small skate (averaging 1-1½ kg. each) were placed in alcohol so as to give about fifty percent. in the mixture, and kept in the refrigerator. The combined pancreases weighed about 120 gm. The extract was prepared in the usual way. A part (160 cc.) of the first obtained filtrate was mixed with alcohol to give about 80 percent., but since only a very slight precipitate formed, the whole filtrate was evaporated in the warmed air current. The final extract measured 22 cc., of which, after standing three days in refrigerator, 10 cc. was injected into small brown rabbit (wt. 1.6 kg.).

Aug. 1st — 9.45 a.m. — 0.120 percent blood sugar.
9.55 " — Injection.
10.55 " — Violent convulsions of the usual type (cf. 10).
11.00 " — Partial recovery.
11.02 " — 0.035 percent blood sugar. No convulsions.
12.00 noon — Again in violent convulsions. Impossible to obtain blood from ear veins. Given about 5 gm. dextrose in solution, subcutaneously. Recovered within 5 minutes.
3.00 p.m. — Quite recovered. 0.064 percent blood sugar.
8.30 " — Appears all right.
Aug. 2 — 9.00 a.m. — Rabbit found dead in cage.

This is the only rabbit of the series in which death occurred after the convulsions had been antidoted by administration of dextrose. The rapid decline in blood sugar to the level at which convulsions occurred, and the death of the animal in spite of injections of dextrose, leave little doubt that an overwhelming dose of insulin had been given.

On *post mortem* examination, the abdominal wall was found a mass of mucigenous material as described by us in a previous paper (loc. cit.).

The remaining 12 cc. of this extract was kept frozen in the refrigerator from August 1st to 22nd, when it was divided into 3 portions, of which one was injected into a rabbit, another heated to 70°C. for 5 minutes, and a third used for chemical examination. The following were the results with the first portion:

Aug. 22 — Albino (clipped) rabbit, wt. 2.75 Kg.
9.00 a.m. — 0.124 percent blood sugar.
9.05 " — 4 c.c. extract injected.
10.25 " — 0.045 percent blood sugar.
11.10 " — Convulsions and coma.
11.15 " — 0.038 }
0.030 }
11.35 " — Much recovered and sitting up.
12.00 noon — Very excitable and on removal from cage there was a convulsive seizure of moderate severity.
12.08 p.m. — 0.033 percent blood sugar.
12.20 " — Injected 2 gm. dextrose.
12.30 " — Animal normal though drowsy.

With the second portion of extract that had been heated the following were the results.

Aug. 22 — Black (brownish hair) rabbit.
9.15 a.m. — 0.112 percent blood sugar.
9.20 " — 4 c.c. extract injected.
10.45 " — 0.038 percent blood sugar.
11.20 " — Convulsions of usual type.
11.30 " — 0.026 percent blood sugar.
11.35 " — Injection of 2 gm. dextrose.
12.00 noon — Rabbit apparently normal.

Heating to at least 70°C. for a period of five minutes does not diminish the potency of the extracts.

The third portion gave no biuret reation although there was a very faint orange tinge by the xanthoproteic reaction.

Experiment V. In this experiment eight small skate were used, of which five, caught on August 2nd, had stood for six days in a cool room and three, caught on August 7, in the basement of the laboratory over night. The excised pancreases were placed in 50 percent. acidified alcohol, in which they stood several days in the refrigerator. After removal from the alcohol the total mass of pancreas weighed 12 gm.. The extract was prepared on August 14 in the usual way, and after

evaporation in warmed air its final volume, including the washings of the tray, was 10 cc., of which 2 cc. was injected into an albino rabbit. (wt. 2.4 kg.).

Aug. 14 — 12.05 p.m. — 0.101 percent blood sugar.
12.10 " — Injection (2 c.c.).
12.40 " — 0.115 percent blood sugar.
2.15 " — 0.079 " " "

The hypoglycæmic effect is not so marked in this case, possibly because of autolytic destruction of insulin before the pancreas was excised.

Experiment VI. The pancreases of four barndoor skate (Raja), averaging 15-16 kg. in weight, were kept in acidified alcohol from August 9th to 14th. (In one of these, weighing 16.4 kg., the pancreas weighed 31.5 gm. moist). The total mass of pancreas after pressing out adherent alcohol with cheesecloth weighed 56 gms. After evaporation, the extract contained much fat which was removed by ether, the fat-free (clear) extract now measuring 15 cc., of which 2 cc. was injected and the remainder passed through a Berkfeld filter and kept 10 days in the refrigerator, when 1 cc. was injected into a rabbit (wt. 2.5 kg.).

Aug. 15 — 11.40 a.m. — 0.122 percent blood sugar.
11.45 " — Injection (2 c.c.).
12.30 p.m. — 0.072 percent blood sugar.
1.55 " — 0.042 " " "

Until 2.30 p.m. no symptoms were noted and the animal was replaced in its cage in the laboratory. On returning to the laboratory at 6.30 it was reported that convulsions had developed about 3 p.m. At 6.30 the animal was in deep coma and almost moribund. About 3 gm. dextrose was injected subcutaneously, with sufficient recovery so that consciousness returned and the animal sat up and tried to hop about. Its movements were, however, incoördinate and it frequently fell to one side. The characteristic movements described elsewhere were very pronounced. Since the condition did not show further improvement, 2-3 gm. dextrose was again given at 7.50 p.m. and in a few minutes the condition markedly improved, the jaw movements disappeared and the animal hopped about

the room in normal fashion. The only symptoms remaining were extreme drowsiness and violent head shaking when lifted by the ears. Next morning the behaviour of the animal was perfectly normal.

The same extract after Berkfelding and standing in the refrigerator gave the following results:

Aug. 24 — 10.45 a.m. — 0.105 percent blood sugar.
10.54 " — Injected 1 c.c. extract.
11.35 " — 0.060 percent blood sugar.
1.35 p.m. — 0.058 " " "

With one half the previous dose a marked reaction is evident, although the hypoglycæmia was not of sufficient degree to be associated with symptoms.

For practical reasons it is important to form some rough estimate of the number of units of insulin (the dosage required to lower the percentage of blood sugar of the normal rabbit to 0.045 within 4 hours; cf.[10]) obtainable from this source of material. This is done in the following table from the data of experiments I, II, IV, V, VI.

Expt. No.	No. of skate	Combined weight of skate used	Weight of pancreas after removal from alcohol (unless otherwise noted)	Proportion of extract injected	Result (units)
I.	(5)	5 kg.	—	all	1
II.	(6)	6 kg.	—	all	½
IV.	(43)	86 kg.	120 gm. (fresh)	5/11 ths	overdose
				2/11 ths	overdose
V.	(8)	8 kg.	12 gm.	1/ 5 th	½
VI.	(4 barn-door)	60 kg.	56 gm.	2/15 ths	1+
				1/15 th	1—

Taking alcohol-preserved pancreas as a basis for calculation, it would appear from the data of Experiment VI that about 1 unit of insulin can be prepared from 4 gm. of raw material. This means that from the pancreas of one barndoor skate, weighing about 15-16 kg., three to four units of insulin can

be prepared ,and from three small skate weighing one kilo or more, one unit. It must be understood that these figures are only roughly approximate, but they are probably sufficient to indicate that insulin can be separated with much greater ease from skate pancreas than from that of oxen. As indicated in Dr. Jackson's paper islet tissue is relatively abundant in this pancreas.

Squalus Acanthias (Dog Fish)

It is to be expected that the closely related dog fish would yield results similar to those of the skate. In the few observations (3) which it was possible to make an extremely potent extract was obtained in one, a moderately strong extract in another, and a practically inert extract in a third.

Experiment VII. The pancreas was removed from seven small dog fish immediately after catching, and placed in 50 percent. acidified alcohol. After standing 24 hours (part of the time in the refrigerator) the extract was prepared in the usual way. It contained much fat which could not be separated by a slow centrifuge. Of a total volume of 35 cc., 10 cc. was injected into an albino rabbit (wt. 2.4 kg.).

Aug. 4 — 10.10 a.m. — 0.110 percent blood sugar.
10.15 " — 10 c.c. crude extract.
11.40 " — 0.098 percent blood sugar.
12.10 p.m. — 0.107 " " "
1.10 " — 0.112 " " "

To the remaining 25 cc., alcohol was added so as to give about 80 percent. in the mixture.. A moderate precipitate separated, which after standing at room temperature for 3 days was collected in a filter, dissolved in water and injected into a brown rabbit (wt. 2.7 kg.).

Aug. 7 — Normal blood not taken.
10.50 a.m. — Injected 8 c.c. solution of precipitate.
12.00 - 12.30 p.m. — 0.115 percent blood sugar (difficulty in collecting blood).
3.30 p.m. — 0.105 percent blood sugar.

Since there was no evidence that the extract was having any effect, the filtrate, after evaporation, was injected into the same rabbit.

Aug. 7 — 3.50 p.m. — Injected 15 c.c. (opalescent) filtrate.
4.35 " — 0.110 percent blood sugar.
5.45 " — 0.100 " " "

There is no evidence in these results of the presence of any insulin.

Experiment VIII. The pancreas was removed from a female dog fish (with pups) weighing 4.4 kg. after the specimen had been dead a few hours. It weighed 10 gm. moist. It was extracted in about 80 percent. alcohol. The final extract (without shaking with ether) measured 14 cc., of which 1 cc. was injected into an albino rabbit (wt. 2.75 kg.).

Aug. 14 — 12.30 p.m. — 0.106 percent blood sugar.
12.40 " — 1 c.c. extract injected.
1.40 " — 0.050 percent blood sugar (Rabbit showing no symptoms).
3.30 " — 0.090 percent blood sugar.

In this case nearly one unit of insulin was obtained from 1/14th of the total extract of one pancreas weighing 10 gm.

Experiment IX. The pancreas was removed from about 20 somewhat undersized dog fish immediately after catching, and placed in alcohol (95%). Since it was thought that the distribution of "islet" tissue might be different in the ventral and dorsal lobes, these were collected and tested separately. After pressing through muslin the total mass of *ventral lobe* pancreas weighed 26.5 gm. The crude extract after evaporation was loaded with fat, which was removed by shaking with ether. The final extract measured 17 cc., of which 10 cc. was injected into a brown rabbit (wt. 2.7 kg.).

Aug. 19 — 10.15 a.m. — 0.102 percent blood sugar.
10.30 " — 10 c.c. extract injected.
11.40 " — 0.062 percent blood sugar.
12.05 p.m. — 0.062 " " "
1.15 " — 0.080 " " "
3.30 " — 0.109 " " "

The result shows that a relatively feeble extract was obtained.
2. *Dorsal lobe.* Weighed 46.5 gm. after pressing through muslin. Volume of final extract 29 cc., so that 10 cc. practically equals 10 cc. of extract of ventral lobe (i.e. is derived from

same mass of pancreas). This was injected into small albino rabbit.

Aug. 19 —	10.50 - 11.05	a.m. — 0.104 percent blood sugar.
	11.10	a.m. — Extract 10 c.c.
	11.55	" — 0.035 percent blood sugar.
	1.30	p.m. — 0.026 " " "
	1.45	" — Left Laboratory.
	2.45	" — On return to laboratory rabbit found in violent convulsions of the usual type.
	3.00	" — 0.042 percent blood sugar.
	3.15	" — 15 c.c. 20 percent dextrose injected. Rabbit soon recovered although it remained very drowsy.
	4.00	" — 0.106 percent blood sugar.
	7.15	" — Rabbit normal but very drowsy. Drank water containing dextrose.
	Next	a.m. — Rabbit normal.

These results would seem to indicate that much more insulin is contained in the dorsal than in the ventral lobe. Specimens of these lobes have been collected for careful histological examination by Dr. Slater Jackson with a view to determining the relative distribution of islet tissue. Taking the results in the former, it is seen that considerably more than one unit was obtained from about 15 gm. of alcohol preserved pancreas.

The Teleostei

As explained in the introduction, the islet tissue is more or less separate from the zymogenous in at least the majority of bony fishes. It is collected into one or several easily recognizable nodules, often encapsulated and associated with relatively little if any zymogenous cells. The latter, on the other hand, exist as thin bands of tissue scattered in the mesentery especially near the pyloric caeca, usually closely adjacent to the branches of the portal vein and sometimes extending with this for some distance into the liver. Specimens of this tissue have been collected by Dr. Jackson for histological examination especially to find out whether it contains any islets. Extracts have been prepared separately from these two sources. After trial of several varieties of fish — Haddock, Hake, Eel, Sculpin and Angler fish — it was decided to pay particular attention to the last two mentioned,

since in them the principal islets are large and easily removable.

Sculpin. Two species were used, Myoxocephalus octodecimspinosus and scorpius. These fish abound along the Atlantic coast, and being voracious feeders they can readily be caught in large numbers by hook and line. They are mostly of small size (up to about 1 kg.) with a large mouth and furnished with many spines. There are usually two principal islets, the largest and most constant of these being situated in the mesentery immediately anterior to the spleen and close by the portal vein. The other smaller islet is situated near the pylorus, and there are usually also several just visible islets scattered here and there in its neighbourhood. The principal islets are of a characteristic pale buff yellow colour.

Zymogenous tissue with no islets visible to the naked eye occurs "as narrow bands adhering to the intestine and occupying the intercaecal spaces" (Rennie).

Experiment X. The principal islets were removed (July 31st) from 35 specimens of Myoxocephalus scorpius and placed in diluted acidified alcohol. After pressing through muslin there was 1.2 gm. of islets. The final extract after removal of the alcohol measured 5 cc., of which 2 cc. was injected into an albino rabbit (wt. 2.4 kg.).

Aug. 1 —	10.00	a.m.	— 0.114 percent blood sugar.
	10.05	"	— Injection.
	11.20	"	— 0.020 percent blood sugar.
	11.30	"	— Rabbit very drowsy, lies on side.
	11.35	"	— Marked convulsions.
	11.45	"	— 0.026 } 0.020 } percent blood sugar.
	11.50	"	— Convulsions less severe.
	12.05	p.m.	— 0.040 percent blood sugar.
	12.10	"	— Convulsions again very severe, so that about 4 gm. dextrose was injected subcutaneously. Recovery was rapid, so that in about 15 minutes the animal ate carrot tops greedily.
	2.30	"	— 0.090 percent blood sugar. Rabbit normal.
	5.40	"	— 0.062 percent blood sugar. Rabbit very hungry.
	6.00	"	— Injected more dextrose.
	Next morning the rabbit was normal.		

The extract was kept in the refrigerator for two days and 1 cc. of it injected into small albino (1.4 kg.) rabbit.

Aug. 3 — 11.30 a.m. — 0.102 percent blood sugar.
11.31 " — Injection.
12.10 p.m. — 0.070 percent blood sugar.
1.30 " — 0.058 " " " (no symptoms).
3.50 " — 0.063 " " "

Extract was also made from a large amount of pancreatic (zymogenous) tissue (true pancreas) dissected out from the same sculpin. The final extract measured 20 cc., and 10 cc. was injected into another albino (unclipped) rabbit.

Aug. 1 — 10.45 a.m. — 0.110 percent blood sugar.
10.50 " — Injection (10 c.c.).
11.35 " — 0.118 percent blood sugar.
12.20 p.m. — 0.115 " " "
1.30 " — 0.124 " " "
2.45 " — 0.156 " " "

The remainning 10 cc. of extract, after being kept 3 days in the refrigerator, was injected into a large brown rabbit (wt. 2.7 kg.)

Aug. 4 — 11.20 a.m. — 0.100 percent blood sugar.
11.30 " — Injected extract.
12.20 p.m. — 0.115 percent blood sugar.
2.00 " — 0.119 " " "

In neither of these observations with extract of zymogenous tissue did the rabbits show any symptoms.

Experiment XI. Principal islets and mesenteric (zymogenous) tissue were removed from 20 specimens of both species of sculpin mentioned above. The fish were caught on the previous evening and had been kept in the basement over night. Extracts were prepared in the usual way. From the islets 9 cc. of extract was obtained, of which 6 cc. was injected into an albino rabbit (wt. 1.64 kg.).

Aug. 8 — 11.00 a.m. — 0.125 percent blood sugar.
11.15 " — Injection.
12.05 p.m. — 0.128 percent blood sugar.
1.15 " — 0.074 " " "
4.45 " — 0.108 " " "

The hypoglycæmic effect, though perfectly definite, is not so marked as in the previous case.

The extract prepared from the mesenteric pancreatic (zymogenous) tissue measured 12 cc., all of which was injected into a black and white rabbit (wt. 2.08 kg.).

Aug. 8 — 10.20 a.m. — 0.110 percent blood sugar.
10.45 " — Injection.
11.45 " — 0.116 percent blood sugar.
12.30 p.m. — 0.114 " " "
1.35 " — 0.105 " " "

As in the previous experiments there was no indication of the presence of insulin in the zymogenous tissue.

Experiment XII. Extract was prepared from the principal islets of 24 Sculpin of both varieties. The total islets, after pressing out adherent alcohol between filter paper, weighed 0.68 gm. The extract stood from August 14th to 25th in the refrigerator, and it measured 12 cc., of which 1 cc. was injected into a black rabbit (2.25 kg.).

Aug. 25 — 12.15 p.m. — 0.092 percent blood sugar.
12.20 " — Injection.
1.30 " — 0.042 percent blood sugar.
2.15 " — Convulsions (these may have occurred earlier) and profound coma.
3.00 " — 0.018 / 0.010 percent blood sugar.
3.10 " — 2 gm. dextrose in 20 percent solution injected. Recovery only partial, so that another 1 gm. dextrose given.
5.45 " — Still not perfectly recovered, being very drowsy, so that another 2 gm. dextrose was given.
Next morning the rabbit was normal.

It is clear from these results that very potent insulin can readily be extracted from the principal islets but not from the zymogenous tissues of sculpin. Apart from its theoretical interest, in throwing light on the question as to whether the source of insulin is the islet or the zymogenous structures of the pancreas, this observation is of practical importance since it shows a possible source of insulin for therapeutic purposes. From 1.2 gm. of alcohol preserved islets decidedly more than three (rabbit) units were obtained in Experiment IX, and from 0.68 gm. (of more thoroughly dried material) considerably more than 12 units were obtained in Experiment XII. The much greater yield of insulin in the last experiment may be

dependent on the fact that stronger alcohol was used and the islets were kept for some time in the refrigerator about 15°C. below freezing point so that they were disintegrated by the formation of ice crystals.

The Angler Fish

(Lophius Piscatorius, also called Monk, Devil or Goose fish).

These fish are conspicuous for the enormous head and mouth and tapering body, an adult specimen being three feet long. An average fish weighs from 13 to 15 kg. Like the sculpin, the angler fish has a very wide distribution on both sides of the Atlantic and it seems to be most abundant at moderate depths, although also present in deep waters. It is caught by long set lines or baited trawls and frequently taken by trawlers. On this side the Atlantic, the angler fish is not used for food — although it is so in Europe — so that the fish are thrown overboard, and it is reported by Connolly that enormous quantities could be landed from the fishing banks of Nova Scotia were there a demand for it. These facts are stated because of the interesting results which will be reported immediately. Rennie (loc. cit.) carefully describes the islets and states that in large fish the principal one may attain the size of the adrenal of the rabbit. In the specimens used in the present investigation two large islets were found, one of which, the largest, was constantly present, as described by Rennie, in the mesentery in the neighbourhood of the spleen, lying between the conspicuously long cystic duct and the duodenum and close by the portal vein. One of the islets after being in alcohol weighed 0.3 gm. Another slightly smaller islet was found nearer the pylorus, and numerous much smaller ones scattered in the upper mesentery in the neighbourhood of the smaller of the principal islets. It should be remarked that in Lophius, as in most of the Teleostei, nematode cysts of varying sizes are not of infrequent occurrence in the mesentery. At first sight these may appear like islets, but even when no nematode can be seen in them their cystic nature and their colour make them readily distinguishable. In the lower mesentery, surrounding the tributaries of the mesenteric and portal veins, bands of pancreatic (zymogenous) tissue occur in which no islets can be distinguished by the naked eye.

Specimens of the islets and of the zymogenous tissue have been collected by Dr. Jackson for histological examination. One structural feature, also observed by Rennie, is the liberal supply of blood vessels.

Extracts were prepared in the usual way from three specimens brought to the station during August.

Experiment XIII. Extracts were prepared in usual way from larger islets of one specimen (not weighed but of average size, i.e. about 14 kg.). The islets were not weighed, but similar ones dissected from another specimen and kept over night in Bouin's fluid and then in alcohol, weighed, after draining off the alcohol, 0.18 gm. The evaporated extract measured 10 cc., all of which was injected into a white and brown rabbit (wt. 2.08 kg.).

Aug. 18 — 11.15 a.m. — 0.098 percent blood sugar.
11.25 " — Injection.
12.25 p.m. — 0.046 percent blood sugar.
1.25 " — 0.048 " " "
2.55 " — 0.064 " " "

The rabbit did not show any symptoms.

Experiment XIV. The principal islets and several of the smaller ones were removed from two specimens of Lophius caught in the weirs on August 21st and kept in the boat for 5-6 hours. The islets were placed in approximately 80 percent. acidified alcohol and kept in the refrigerator over night, so that they were frozen. On removal from the alcohol, the total tissue weighed 1.15 gm., the largest islet weighing 0.3 gm. After maceration in the alcohol, filtration was very slow, so that the more solid tissue was removed by using a water centrifuge. The supernatant fluid, with washings, after evaporation was 2 cc., with a considerable amount of greasy residue. This was diluted with water to 12 cc., filtered, and 2 cc. of the filtrate used for injection into a rabbit of average weight.

Aug. 23 — 10.45 a.m. — 0.108 percent blood sugar.
10.50 " — Injection.
12.00 noon — 0.042 percent blood sugar.
12.40 p.m. — Rabbit hyperexcitable and on removal from cage developed convulsions.
12.45 " — 0.024 percent blood sugar.

12.47 " — Injected 2 gm. dextrose.
1.20 " — 0.054 percent blood sugar. Rabbit apparently normal.
3.20 " — Rabbit again in convulsions.
3.25 " — 0.025 percent blood sugar.
3.30 " — Injected 2 gm. dextrose. After this and during the evening the animal was normal though drowsy.
Next morning — Rabbit normal.

In this experiment considerably more than one (rabbit) unit of insulin was therefore obtained from about 0.19 gm. of alcohol-soaked islet.

From the same two fish pancreatic (zymogenous) tissue in which no islets could be seen was dissected from the lower mesentery and an extract prepared by exactly the same procedure as used for the islets. Five cubic centimetres of a somewhat muddy extract was obtained, and all of it was injected into an albino rabbit (wt. 2.4 kg.).

Aug. 23 — 11.05 a.m. — 0.124 percent blood sugar.
11.15 " — Injection.
12.15 p.m. — 0.125 percent blood sugar.
1.15 " — 0.110 " " "
3.40 " — 0.112 " " "
At no time did the animal show any symptoms.

The very definite nature of these results leaves little doubt that *insulin is present only in the islet tissue and not in the zymogenous*, although more specimens of this fish must be examined before this can be positively asserted.

With regard to the practicability of preparing insulin from this source, it may be stated that this is being tried. The advantages are that the fish is readily procurable, the islets can be recognized and removed by unskilled assistance, very little alcohol is required for preparation of the extracts, and, as shown in Experiment XIV, at least from 3 to 4 (rabbit) units of insulin can be obtained from one fish.

The Eel Pout
(Zoarces anguillaris)

Rennie states that in the related species, viviparus, a principal islet, free from zymogenous tissue, occurs near the spleen in a triangle formed by the mesenteric and hepatic arteries

and the portal vein. In this position a principal islet also occurs in the small closely related gunnell (Pholis gunnellus) and this has been carefully examined by Rennie. A sufficient number of specimens were not brought to the station from which to collect principal islets. Zymogenous pancreatic tissue which, mixed with a considerable amount of fat, is plentifully distributed in the mesentery, was however removed from several specimens and extracts prepared in the usual way.

Experiment XV. The mesenteric pancreas from zoarces, along with some of the corresponding tissue from several specimens of sculpin, yielded 10 cc. of extract, which was all injected into a small albino rabbit (wt. 1.58 kg.).

July 24	10.35 a.m.	— 0.104 percent	blood sugar.
		Injection.	
	12.15 p.m.	— 0.098 percent	blood sugar.
	2.00 "	— 0.113 "	" "
	3.30 "	— 0.140 "	" "

There is no evidence of the presence of insulin.

Experiment XVI. The mesenteric pancreas of 4 specimens of zoarces was extracted after standing in alcohol in the refrigerator. The final extract amounted to 15 cc., all of which was injected into a black rabbit (wt. 2.75 kg.).

Aug. 12	10.50 a.m.	— 0.142 percent	blood sugar.
	10.55 "	— Injection.	
	11.25 "	— 0.128 percent	blood sugar.
	12.15 p.m.	— 0.107 "	" "
	1.15 "	— 0.106 "	" "

The normal blood sugar in this rabbit was unusually high (probably postprandial) and it steadily declined during the period of observation. This makes it difficult to decide whether the extract had any hypoglycæmic effect, but this is very unlikely since the blood sugar never went below the level usually found to be the normal.

The results of these two experiments confirm the conclusion already drawn from the experiments on Myoxocephalus and Lophius, that the zymogenous pancreatic tissue of the mesentery does not contain insulin. We must await the histological report, however, before drawing final conclusions.

A number of observations were also made with extracts prepared from other sources than the foregoing, and the chief of these, in so far as they relate to the main problem, will now be briefly reported.

Liver of Myoxocephalus.

Experiment XVII. Since pancreatic tissue extends in many teleostei into the liver, an extract was prepared from the livers of several sculpin. Pieces were also set aside for histological examination. The extract took considerable time to evaporate because of the large amount of water which it contained. The injection (10 cc.) was made into a male brown rabbit (2.7 kg.).

July 26 — 12.10 p.m. — 0.122 percent blood sugar.
12.15 " — Injection.
1.15 " — 0.128 percent blood sugar.
3.20 " — 0.132 " " "

There was no evidence of any hypoglycemic effect.

Pancreas of Anguilla

Experiment XVIII. In the eel (Anguilla vulgaris) there is a fairly dense band of pancreatic tissue running along a main branch of the portal vein parallel to the first portion of the small intestine. No principal islets could be seen in this animal and it is possible that the islet tissue is scattered among the zymogenous as in the Elasmobranchs and the higher vertebrates. An extract was prepared from this pancreatic tissue removed from about 20 large specimens of this fish, some also being taken for histological examination. The tissue was kept for some days in alcohol in the refrigerator, and the final extract measured 7 cc., all of which was injected into an albino rabbit (wt. 2.250 kg.) that had been injected on the previous day with a highly potent extract of dog fish pancreas (see Experiment VIII).

Aug. 26 — 12.30 p.m. — 0.088 percent blood sugar.
12.35 " — Injected.
2.50 " — Mild convulsions and rabbit semi-conscious.
2.55 " — 0.020 percent blood sugar.

3.45 " — Since the last blood sample, the rabbit had been comatose with occasional convulsive seizures. 0.020 percent blood sugar.
3.53 " — Injected 2 gm. dextrose.
5.03 " — The rabbit was completely recovered and an unsuccessful attempt was made to obtain a sample of blood.

The mesenteric pancreatic tissue of the Eel therefore yields much insulin. The relatively low normal blood sugar of this rabbit may have been due to a prolonged influence of the dog fish extract that was injected on the previous day.

Remarks.

These investigations taken as a whole show quite clearly that insulin is present in relatively great amounts in extracts prepared from the pancreas of representative Elasmobranch fishes (Squalus and Raja) and from the principal islets of representative Teleostean fishes (Myoxocephalus and Lophius) whereas it is absent in extracts of the mesenteric pancreatic tissue (zymogenous cells) of the last mentioned fishes and also of Zoarces. This result would seem to afford direct proof for the hypothesis that insulin is derived from the islets, but we must await the report of the histological examination of the tissues used for preparation of these extracts before the question can be considered as finally settled. When, however, this direct proof is taken along with the indirect evidence referred to in the introduction to this paper, the case for the insular hypothesis becomes very strong indeed.

It is difficult to see at present why insulin should be relatively so abundant in the fishes. The food of those used in this investigation consists almost entirely of smaller fishes or crustaceans, so that its carbohydrate content is relatively low. On the other hand the blood of both the cartilaginous and the bony fishes contains reducing sugar in amounts not much, if any, lower than that found in the blood of mammals, and there are often large amounts of glycogen in the liver (cf. Kilbour, Lang and Macleod, and E. L. Scott[10]), all of which would seem to indicate that carbohydrates play as essential a part in the metabolism of fishes as they do in that of mammals. It is difficult to see where this carbohydrate can be derived from, unless it be from protein, for it is scarcely conceivable

that the carbohydrate ingested from vegetable sources by the lowest forms of aquatic organisms can, after transfer through crustacea and smaller fishes, serve as its source in the larger fishes. Another feature of many fishes is the remarkable degree to which fat (oil) may become deposited in the liver and other tissues. Is it possible that the transformations from one kind of proximate principle into another is regulated by insulin?

Quite apart from their theoretical interest, the results also have a practical value, for they show that insulin can be prepared by very simple and inexpensive methods from the principal islets of certain readily available fish, Lophius and Myoxocephalus. This possibility had previously been tested by Rennie and Fraser, who failed to demonstrate the presence of insulin mainly because they administered the islets by the mouth, either in the raw state or as saline extracts. We know that insulin is readily destroyed by digestive enzymes, and in yet unpublished researches it has been found that insulin is inactive when given by this pathway. Before insulin prepared from fishes can be freely used for therapeutic purposes, it remains, of course, to show that the hypoglycæmic effect demonstrated in this research on normal rabbits also occurs in diabetic animals and in man, but there can be little doubt that this will prove to be the case, and it will be tested immediately.

I wish to express my thanks to the Biological Board of Canada for placing the splendid facilities of their Atlantic Station at St. Andrews at my disposal for this investigation, and to Dr. Huntsman, its director, for his courteous assistance and his helpful criticism throughout the work.

Conclusions.

1. Potent insulin preparations were readily made from the pancreas of the cartilaginous fishes — the dog fish (Squalus acanthias) and the skate (Raja).

2. Still more so was this the case with the principal islets of Rennie, which are found in many of the bony fishes, the Angler (Lophius) and the sculpin (Myoxocephalus). Since these are readily available fishes, they may serve as a practical source of insulin.

3. No insulin could be prepared from the pancreatic tissue proper (zymogenous or acinar) of the representative bony fishes (Lophius Myoxocephalus and Zoarces).

Although the anatomical relationships of these tissues are still somewhat obscure, the above results afford strong direct evidence for the hypothesis that insulin, as its name implies, is derived from the insular and not the zymogenous tissue of the pancreas.

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PHYSICAL MEASUREMENTS OF DIABETIC PATIENTS

With a Discussion of Normal Weight Standards. *

by H. F. ROOT, M. D., and W. R. MILES, Ph. D.

INTRODUCTION

Evidence steadily accumulates from clinical studies, insurance and military experience, and from vital statistics, which demonstrates the importance of the relationship between disease and deviations from normal nutritional condition as represented by body-weight. Joslin[1] has shown that men who are 6 to 20 per cent over weight are from 6 to 20 times more liable to diabetes than are individuals of the same age 6 to 20 per cent below standard weight. In this comparison he has made use of the Medico-actuarial Weight Tables[2]. A new set of suggested weight standards has recently become available, *i. e.*, those published by Dreyer and Hanson[3], which predict normal weight on the basis of stem length and chest girth in place of the usual height and age factors. Dreyer and Hanson also offer tables for normal vital capacity which, together with their weight standards, they recommend as means for estimating the "physical fitness" or degree of bodily vigor. Gray and Root[4] were the first to demonstrate that the Dreyer weight standards correspond most closely with the observed weights of supposedly normal adults, and they pointed out certain defects in the Dreyer method. Dublin[5] and Fisk[6] have offered further important criticisms of the Dreyer formulae and conceptions. A discussion of these points cannot be entered into here. We have used Dreyer's tables without modification. We are not aware that this his standards have been employed in the study of any considerable group of pathological material. The discussion of obesity in diabetes by Joslin has suggested to us the desirability for such an application in the careful examination of diabetic individuals.

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Our first interest, them, has been to study certain physical measurements of a group of diabetic patients as compared with two sets of "normal" weight standards. For this purpose our patients have been divided first as to sex, and then successively as to age, duration of diabetes, loss of weight, and the severity of the diabetes as indicated roughly by the carbohydrate tolerance. A previous study has indicated that diabetic patients are somewhat below normal in memory, power of concentration, and speed of neuro-muscular reactions[7]. It is well known that severe diabetes produces emaciation and loss of muscular power, but since our group on which physical measurements were made includes many mild cases, conclusions may be drawn as to whether patients of all degrees of severity give evidence of lowered physical efficiency. Dreyer has stated that the vital capacity is of fundamental importance in relation to the physical well-being and we have investigated whether in diabetes it varies greatly from normal. Our data may therefore be conveniently discussed in connection with the following problems:

1. Are deviations from normal physical measurements associated with diabetes?
2. What degree of physical vigor has the average diabetic as compared with Dreyer's standards?
3. What physical measurements appear to be the most useful for predicting normal weight and in assessing the physical condition of a diabetic patient or others suspected of prolonged nutritional disturbance?

SUBJECTS AND MEASUREMENTS

The study was made between January and August, 1921 on a group of 133 diabetic patients at the New England Deaconess and Corey Hill Hospitals. The individuals varied in age from 16 to 70 years and represented all degrees of severity of the disease. In a few instances the patients were not actually in the hospital wards at the time, but had merely returned for follow-up treatment. No effort was made on our part to select the material in any way, except that the few cases with pulmonary tuberculosis and definite cardiac disease were excluded.

The following measurements were obtained:

1. *Height* was always measured without shoes except in a very few cases, and in these a correction was made for heels. The patient stood upright on a level surface with the back against a measuring post. The height was taken with the head neither tilted up nor down and with the eyes looking straight forward.

2. *Trunk or stem length.* Patients were directed to sit on the floor with the back against a measuring post, then with the backs of the fingers resting on the floor the body was raised, bent forward and the sacrum thrust against the measuring post. The hands were placed in the lap, and with the patient sitting upright, the height to the vertex was taken. * This measure is called also "stem length".

3. *Chest circumference.* This measure was taken according to Dreyer's direction, at the nipples in men and below the mammary tissue in women. The measure was taken while the patient was answering some simple question, ("resting girth") and thus does not represent the circumference at either maximum inspiration or expiration, but as shown by Gray[8] is ussually a little less than the mean of these.

4. *Body-weight.* The weights of all patients actually in the wards were taken about 6 a. m., with the subject nude, empty bladder, and in the post-absorptive state. In a few cases the weight was taken during the course of the day. Correction was then made for clothing.

5. *Vital capacity.* A dry gasmeter, such as is recommended by Dreyer, was used for this measurement. The patient stood and made five trials, the highest of which was recorded as the score. Usually the third of the five trials gave the highest value. Practically all the tests were made when subjects were wearing loose clothing.

In using the term "*carbohydrate tolerance*" when determining the severity of the diabetes, we mean the amount of carbohydrate as such in the diet which may be taken by the patient without glycosuria. We realize that the expression "carbohydrate tolerance" is a rather loose one, but the figures as given do correspond roughly with a clinical estimate of the patient's tolerance. By *glucose tolerance* is meant the

* We followed the method of Dreyer and used the same sort of a measuring device. See Dreyer and Hanson, *The Assessment of Physical Fitness*, London, 1920, p. 6, Fig. 1. This device we used also for taking the heights.

sum of the carbohydrate of the diet, 60 per cent of the protein and 10 per cent of the fat, from which is subtracted the glucose in the urine. In certain severe cases allowance was made for glucose derivable from lost tissue protein according to Woodyatt's method[9]. Data as to the duration of the diabetes and the maximum body-weight were obtained from the patients' histories which Dr. E. P. Joslin has kindly made available to us. It is recognized that these are the least exact items in spite of particular efforts to ascertain the facts in each case. Correction has of course been made for clothing so that all the weights are net, *i. e.*, without clothing.

METHODS OF COMPARISON OF PHYSICAL DATA

Our comparisons of subject-material are of two kinds:

1. Diabetics as an average group (men and women being considered separately) as compared with normal standards. The standards chosen to serve us in the stead of normal individuals were: (a) Dreyer and Hanson standard, which gives normal body-weights for trunk length and chest girth; normal chest girth for trunk length; and normal vital capacity calculated for body-weight, trunk length, and chest girth. (b) Medico-actuarial standards[2] based on life insurance material for the factors of height and age. These actuarial standards are commonly used in medical literature and may be compared with the individuals at present, and, by assuming in adults no change in height, can be compared with the past maximum weight.

2. One group of diabetics is compared against another group which differed in average age, duration of the disease, weight loss from previous maximum, or average carbohydrate tolerance at time of observation. Two such groups have been made under each one of these heads. Our material was not large enough to permit of a greater number of such divisions, although it is higly desirable. The dividing line in each case has been rather arbitrarily chosen at such a point that it would divide the individuals of each sex group into sub-groups approximately equal in number. The carbohydrate tolerance of the women was considerably below that of the men, hence a different dividing line was set for the two sexes in this comparison.

The averages for the physical data obtained are given in

table 1 for the men and in table 2 for the women. Both tables are identical in arrangement and include the entries and calculations in such an order as will facilitate reference to the data. The entries and calculations represented in each of the 28 lines of the two tables were made for each patient as if he or she were the only one being studied. The tables are therefore made up entirely of averages, even to all predictions and ratios. The possible comparisons are very many. We assume that readers particularly interested in diabetes can readily understand the tables and draw their own conclusions in reference to points which cannot be considered in this paper.

TABLE I.

The physical measurements for diabetic men.

Diabetic Men	Age groups			Duration of Diabetes		Weight Loss from Maximum			Carbohydrate tolerance	
Average measurements and comparisons	All ages	48 yrs and under.	Over 48 years	2 yrs and under	Over 2 years	21 per cent and under	Over 21 per cent	Never over weight	1.5gm. per kg. and under	Over 1.5gm. per kg.
Total No. of cases	77	46	31	35	42	40	37	20	38	39
Average age, years	41	31	57	34	47	36	47	28	44	39
Duration of diabetes, yrs.	5.0	4.0	6.7	1.3	8.2	4.8	5.3	4.1	4.9	4.9
Date of max. weight	1914	1917	1911	1918	1912	1916	1913	1918	1914	1915
Carb. tolerence, gms	105	115	93	121	94	122	87	105	56	153
Tolerance per kg. of wt.	1.7	2.1	1.4	2.0	1.4	2.0	1.4	2.0	0.9	2.5
Glucose tolerance per kg.	2.6	2.9	2.2	2.9	2.4	2.8	2.3	3.0	1.9	3 3
Height, net in cm	171	171	170	171	171	170	172	17.2	172	170
Variability of ht., p. ct.	3.5	4.0	2.6	3.6	3.3	4.1	2.8	5.1	3.3	3.7
Trunk (Dreyer) in cm	88.9	88.8	89.2	89.1	88.8	88 6	89.3	88.6	89.4	88.5
Variability of trunk, p. ct.	3.3	3.5	2.8	2.9	3.5	3.5	2.7	4.3	3.4	3.2
Ratio trunk to height	52.0	51.9	52.4	522	51.9	52.2	51.9	51.6	52.0	52.1
Chest circum. (Dreyer cm)	87.4	83.0	94.0	86.8	88.0	86.7	88.1	78.9	87.3	87.7
Variability of chest p. ct.	7.9	6.5	5.2	8.3	7.5	7.4	8.3	6.5	8.0	7.5
Predicted chest from trunk	84.9	84.7	85.2	85.0	84.8	84.7	85.2	84.7	85.4	84.4
Observed net weight kg.	61.2	56.1	68.0	60.3	61.4	61.5	60.6	51.9	60.6	61.2
Variability of wt., p. ct.	15.4	14.8	13.4	15.3	15.3	13.8	16.5	14.3	16.7	14.2
Predicted wt. from chest	68.8	59.6	82.5	67.7	69.7	66.7	70.8	51.7	68.7	68.9
Predicted wt. from trunk	62.6	62.3	63.0	62.9	62.4	62.2	63.3	62.2	63.6	61.6
Dreyer's standard wt.	65.7	60.9	72.6	65.2	66.0	64.4	66.9	56.8	66.1	65.2
Actuarial standard wt.	67 0	65.1	69.9	65.2	68.6	65.1	69.4	64.9	68.5	65.6
Ratio obs. wt. to Dreyer wt.	92	92	94	93	93	96	91	91	92	94
Ratio obs. wt. to Actu.[1] wt.	91	86	97	93	90	95	87	80	89	93
Maximum reported wt.	78.1	70.3	89.9	74.2	80.9	71.8	85.5	61.2	79 3	76.2
Ratio obs. wt, to max. wt.	78	80	76	81	76	87	71	85	76	81
Loss from max. wt, p. ct.	22	20	25	19	24	13	29	15	24	19
Actul. wt. at date of max.	65.7	63.8	68.5	64.1	66.9	63.9	67.9	63.9	67.2	64.2
Ratio max wt. to Actu.[1] wt.	119	110	131	116	121	112	126	96	118	119
Vital capacity in c. c.	3990	4047	3862	4130	3901	4040	3976	4050	3881	4161

[1] Medico-Actuarial standard.

TABLE II.

The physical measurements for diabetic women.

Diabetic Women Average measurements and comparisons	Age groups			Duration of Diabetes		Weight loss from maximum			Carbohydrate tolerance	
	All ages	48 yrs and under	Over 48 years	2 yrs and under	Over 2 yeaas	21 per cent and under	Over 21 per cent	Never over weight	0.8 gm per kg. and under	Over 0.8gm. per kg.
Total no. of cases	56	27	29	25	31	25	29	16	27	29
Average age yrs.	47	39	57	43	50	43	50	41	41	47
Duration of diabetes yrs.	4.2	3.4	4.9	1.3	6.5	4.0	3.9	2.1	4.1	4.6
Date of max. weight	1914	1915	1913	1917	1911	1913	1914	1915	1913	1913
Carb. tolerance, gms.,	62	54	68	68	57	78	4.8	52	28	93
Tolerance per kg. of wt.	1.1	1.0	1.2	1.3	1.0	1.4	1.1	1.2	0.5	1.7
Glucose tolerance per kg.	1.9	1.9	1.9	1.9	1.9	2.1	1.8	2.0	1.4	2.3
Height, net in cm.	159	162	157	160	1.60	160	159	158	160	159
Variability of the ht. p. ct.	2.9	2.2	3.1	2.6	2.6	2.7	2.8	3.4	3.1	2.5
Trunk (Dreyer) in cm.	84.5	85.2	83.8	84.3	84.6	84.3	84.8	82.9	85.0	84.1
Variability of trunk p. ct.	3.1	2.8	3.6	2.8	3.0	3.4	3.1	2.8	3.1	3.2
Ratio: trunk to height	52.9	52.7	53.2	52.8	53.0	52.6	53.4	52.4	53.2	52.8
Chest circum.(Dreyer) cm.	75.7	72.5	78.9	74.3	77.1	76.5	75.0	68.6	74.5	77.1
Variability of chest p. ct.	9.0	7.9	8.4	9.4	7.4	9.4	8.1	4.8	8.5	8.8
Predicted chest from trunk	73.6	74.1	73.0	73.4	73.6	73.4	73.8	72.3	73.9	73.2
Observed net weight kg.	53.9	51.1	56.6	52.4	54.9	57.6	49.9	42.1	51.8	55.6
Variability of wt. p. ct.	19.7	20.9	17.7	20.5	18.9	19.3	20.1	13.3	19.9	20.7
Predicted wt. from chest.	65.0	54.4	74.4	61.6	67.9	64.8	62.2	44.0	60.9	67.2
Predicted wt. from trunk.	55.5	56.9	54.3	55.1	55.9	55.2	56.1	52.5	56.5	54.7
Dreyer's standard wt.	60.3	55.7	64.4	58.4	61.9	60.5	59.2	48.3	58.4	62.2
Actuarial standard wt.	61.4	60.2	62 6	61.0	62.4	61.0	60.0	59.2	61.6	61.2
Ratio: obs. wt.to Dreyer wt.	88	92	88	90	89	9[illegible]	84	87	89	89
Ratio: obs. wt. to Actu.[1] wt.	89	85	90	86	88	94	83	71	84	90
Maximum reported wt.	71.1	64.5	76.9	68.5	73.4	67.8	73.9	53.7	72.6	69.9
Ratio: obs. wt. p. ct.	76	77	74	77	75	85	68	77	72	80
Loss from max. wt. p. ct.	24	23	26	23	25	15	32	22	28	20
Actul. wt. at date of max.	59.7	58.3	61.0	59.2	60.2	58.7	60.6	57.5	60.2	59.3
Ratio: max wt. to Actu.[1] wt.	119	111	126	116	122	115	122	94	121	118
Vital capacity in c. c.	2336	2589	2155	2475	2251	2385	2302	2177	2361	2237

1 Medico-Actuarial standard.

DIABETIC MEN AND WOMEN COMPARED

For the general comparison of diabetics with normal standards, the reader is referred to the colums headed "All ages" in each table. We are dealing in this discussion with 77 men whose average age is 41 years, and 56 women whose average age is 47 years. The average duration of the diabetes at the time of measurement in 1921 is 5.0 years for the men and 4.2 years for the women. The average date of maximum weight for both sexes is 7 years previous to observation, 1914. The average carbohydrate tolerance is 105 and 62 grams, respectively for men and women. In terms of per kilogram

of body-weight, which is the more logical way of comparing carbohydrate or glucose tolerance, the men show for carbohydrate 1.7 and the women 1.1 gms. per kg. while for the total glucose tolerance we find 2.6 and 1.9 gm. The male and female groups are closer together for total glucose than for carbohydrate tolerance. The 77 men have an average height in round numbers of 171 cm. with a coefficient of variability (average mean variation for the series divided by the average height) of 3.5 per cent. The trunk length is 88.9 cm. with a variability of 3.3 per cent, and the ratio of the trunk length to height is 52.0 per cent. If for comparison values, we consult Army Anthropology[10], it will be found that the mean height for the United States recruit is given as 172 cm. with a variability of 3.9 per cent; sitting height, 90.4 cm., with a variability of 3.9 per cent, and ratio of trunk to height, 52.0 per cent. The diabetic women in our series show for average height, 159 cm. with a variability of 2.9 per cent; for trunk length, 84.5 cm., with a variability of 3.1 per cent, and for ratio of trunk length to height, 52.9 per cent.

The average chest circumference for the men is 87.4 cm., with a variability of 7.9 per cent, while for the women, it is 75.7 cm. with a variability of 9.0 per cent. Using the trunk length and predicting the chest girth that would be expected, we find from Dreyer's tables an average for the men of 84.9 cm., and for the women 73.6 cm. Judged on this basis, both men and women at the time of measurement show chest girths about 3 per cent larger than would normally be expected.

The average observed weight for men is 61.2 kg., with a variability of 15.4 per cent. The women show an average of 53.9 kg., with a variation of 19.7 per cent. According to the Dreyer and Hanson tables, the men judged by the observed chest girth, would be expected to have a body-weight of 68.8 kg. and according to the trunk length, a weight of 62.6 kg. The Dreyer standard weight (average of predictions from chest and trunk) for these individuals would therefore be 65.7 kg. The actuarial standard weight which applies here would be 67.0 kg. Thus, in the case of the men, the observed weight amounts to 92 per cent of the Dreyer standard, and 91 per cent of the actuarial standard weight. It will be seen that the body-weight predicted from chest girth is the farthest

above the observed weight, indicating that the chest girths of the men were larger than would be expected, as has already been shown in the previous comparison of the chest girth and trunk length. The women show parallel results except that their weight is 89 per cent of the Dreyer standard and 88 per cent of the actuarial standard. The men are therefore 8 to 9 per cent under the standard present weight expectancy while the women are 11 to 12 per cent below. The maximum weights reported by the men average 78.1 kg., therefore the weights observed at the time of the study (61.2 kg.) average only 78 per cent of their previous highest weight, showing a loss from maximum of 22 per cent. The women reported on the average a maximum weight of 71.1 kg. Their observed weights (53.9 kg.) therefore average 76 per cent of their previous maximum, with a loss of 24 per cent. The actuarial weight, supposedly standard for the height and the age when the maximum weight individually occurred is 65.7 kg. for men and 69.7 kg. for women. Both sexes thus show that according to actuarial standards their maximum weight was 119 per cent of their normal weight at that time or that both groups were on the average 19 per cent overweight, whereas their observed weights at the time of the study are 22 and 24 per cent, respectively, below maximum.

The women of our series show a more severe diabetes on the average than the men. Both sexes have been overweight by an equal amount and at a period about equally removed from the date when our measurements were taken. The women show slightly greater loss in weight from their maximum and are somewhat more below the predicted standard on the basis of trunk, chest, height, and age. They have a considerably smaller tolerance per kilogram of body-weight in spite of the fact that the diabetes is of shorter duration and that on the average they are somewhat older.

Conclusion: Diabetic patients have normal stature but the disease is physically characterized by changes in body-weight, being preceded by a condition of obesity amounting to approximately 19 per cent above average normal weight succeeded by a weight loss from maximum of 22 to 24 per cent, and from the normal expected weight of the individual of 8 to 11 per cent 4.6 years after the onset. Patients that

come for treatment in this clinic have on the average a carbohydrate tolerance of about 1.5 gms. per kg. of body weight. *

Age grouping

There are 46 men and 27 women in this series who are 48 years old or younger and 31 men and 29 women who are older than 48 years. Tables 1 and 2 show that the diabetes was of longer duration with the older groups, being 6.7 years for the men, and 4.9 years for the women. The carbohydrate tolerance per kilogram of body-weight is different for the two age groups but does not run parallel for the two sexes. The younger men show 2.1 as against 1.4 gms. for the older men, while the women show 1.0 and 1.2 gms., respectively. The total glucose tolerance per kilogram for both groups of women is the same, 1.9; the two male groups differ in the same direction as with carbohydrate but not to as great an amount. In most other respects, the two age groups for the two sexes show similar tendencies. The chest circumference for the older group is in each case considerably larger than that for the younger group and larger also than the chest girth predicted from the trunk length. For the younger diabetic men and women, the predicted chest girth is in both cases slightly larger than the observed chest circumference.

The older diabetics also show a considerably greater average weight than the younger group. The observed weight of the older diabetics is higher than the weight predicted from the trunk length by 2.3 kg. for women and 5.0 kg. for men, but is considerably below their weight predicted from chest girth, *i. e.*, 17.8 kg. for women, and 14.5 kg. for men. The Dreyer standard weight for older diabetics is with both sexes higher

* In comparing different diabetic groups we may eliminate any further discussion of stature. As may be seen from tables 1 and 2, among the men the height is very closely the same for all of the different groups which are shown. The trunk length also appears to be the same or not significantly different. The percentage variabilities for height and trunk averages are closely the same and relatively very small as we shall have occasion to point out later on in this paper. In the case of the women there is slightly more difference between the average heights for the different diabetic groups. The largest difference is in the age group, as the women 48 years and under have an average height of 162 cm., while women over 48 years average 157 cm., a difference of 5 cm. The difference between the same two age groups for the men is only 1 cm. but in like direction. The older men and women may reasonably be expected to show less average height. Probably the difference for the women is larger than normal and may be credited to accident in this case. The ratio of trunk to height is fairly constant at about 52 to 53 per cent. The women show a higher average ratio by about one point as usually recognized in the literature on normals. It happens that with both sexes, the individuals over 48 years of age have slightly higher trunk-height ratios, indicating longer trunk or shorter legs than individuals 48 years or younger.

than the observed weight and also higher than the actuarial standards for the same patients. The older women show a ratio of observed weight to Dreyer weight of 88 per cent and to actuarial weight of 90 per cent, while the older men show ratios of 94 and 97 per cent, respectively. With the younger diabetics, who weigh considerably less than the older ones, the situation is reversed. With both men and women in the younger group, the weight predicted from actual chest girth is less than that predicted from trunk length. Their chests are smaller than would be expected and the Dreyer standard weight for them thus more closely corresponds to the observed weight, reflecting as it always does through the chest circumference the present condition.

By reference to the data for maximum weight, we see that there is quite a difference between the two age groups. The older diabetics have been considerably more obese, showing ratios between maximum weight and actuarial weight at the time of maximum of 131 per cent for the men and 126 per cent for the women, as against 110 and 111 per cent for men and women 48 years and younger. The older patients have lost the greater amount from maximum weight, these losses being 24 per cent for the men and 26 per cent for the women, while the younger patients show losses of 20 and 23 per cent for men and women, respectively.

Conclusion: Our diabetic patients over 48 years of age give a history of greater obesity than those below that age. On the average the older patients have been 25 or 30 per cent. over weight and the younger ones about 10 per cent. over expected actuarial weight. Both groups have lost 20 to 25 per cent. of their maximum weight, the older group having lost somewhat the more. At the time of measurement, the different age and sex groups were from 3 to 15 per cent. under weight according to the two standards used. The women, particularly the older women, are most under weight. Differences in weight usually have their counterpart in corresponding differences in chest circumference. Therefore Dreyer's method actually takes age into account indirectly, since as obesity develops in middle life the chest circumference increases, and hence the weight predicted from the chest increases. The older diabetics indicate that at the time of their obesity the chest circumference increased but as they lost weight the decrease in

chest circumference has not quite kept pace. We know but little about the time relations of these changes.

MEASUREMENTS IN RELATION TO SEVERITY

Duration.

When both sex groups are divided at the point of two years' duration of diabetes, there are 35 men and 25 women who have had recognized diabetes for 2 years or less and 42 men and 31 women whose diabetes was of more than 2 years' duration. The two groups show similar relationships for both men and women. Those with diabetes for more than two years are in general 7 or more years older, and have less carbohydrate tolerance, (*glucose tolerance being more nearly constant*) but show larger chest and greater average observed weight than the more recent cases. The groups with longer duration, both men and women, have been more overweight and have lost the greater percentage of weight. As in our other comparison, the women demonstrate a weight condition at the time of measurement less favorable than that found with the men.

To sum up, we may say that cases of long duration are those associated naturally with greater age at onset, somewhat greater preliminary obesity, a carbohydrate tolerance growing less with extended duration with the result that the patients lose a somewhat greater proportion of what has been their maximum weight, and reach an average level of about 90 per cent. of their expected weight at the time of measurement.

Observed loss from Maximum Weight

There were 37 men and 29 women who had lost more than 21 per cent of their maximum weight and 40 men and 25 women who had lost 21 per cent. or less, with average differences of 11 and 7 years for men and women, respectively, between the ages of the two groups. At the time of examination, no patient excepting one adolescent boy, was at his maximum weight. The men show ratios of observed weight to maximum weight ranging from 58.6 to 96.0 per cent., the women from 52.4 to 98.0 per cent. The duration of diabetes shows very slight change in the two groups for either sex but the carbo-

hydrate and total glucose tolerances are smaller in those cases with whom the weight loss has been greatest. The women with more than 21 per cent loss have chest circumferences 1.5 cm. less, and average weight 7.7 kg. less, than those who have not lost so much weight. The differences in these measurements are small for the men. With both men and women, those who have lost most have been considerably more overweight, as the average ratio of maximum weight to actuarial weight for the two groups of men is 112 and 126, and for the two groups of women, 115 and 122. The men have lost 13 and 29 per cent from maximum, and the women 15 and 32 per cent. for the respective groups. Patients at the time of measurement were nearer to their Dreyer standard than to their actuarial standard.

The "never over-weight class"

Are there adult diabetics who have never been over-weight? If we examine the next to the last line in tables 1 and 2, it will be found the rule for all of our groups, both men and women, to show an average ratio of maximum reported weight over actuarial weight at the time of maximum which is from 110 to 131 per cent., *i.e.*, no matter what grouping is used for the diabetic patients whom we have measured, it appears that they have on the average, been over-weight when judged by the liberal standard of the Medico-actuarial Tables. There are, however, several individuals among both men and women whose maximum weight has never reached the actuarial expectancy or at least has never been more than 5 per cent. above that figure. These individuals warrant special consideration.

Among the 77 men measured, there were 20 whose maximum reported weight ranged from 74.1 to 105.0 per cent. of their actuarial expected weight and averaged 96 per cent. There were 16 women among the 56 measured whose similar ratios ranged between 70.4 and 104.0, with an average of 94 per cent. The women in this group were considerably older than the men, 41 as compared to 28 years. The duration of diabetes for the women was 2.1 as compared with 4.1 years for the men, but the men show a somewhat higher tolerance per kilogram of body-weight, *i.e.*, 2.0 as compared to 1.2 gm. The relative tolerance with men and women is about the same as that shown

in the other groupings. It is noteworthy that these two groups show conspicously small chests, in fact, the smallest for any of the groups. The same may be said in reference to the observed weight. The 16 women average only 42.1 kg. as compared with the usual weight of 50 or more kilograms. The 20 men average 51.9 kg. in body-weight as compared to 60 or more kilograms which is found, on the average, for the other groups, with the single exception of 55.1 kg. for the men 48 years or younger. We have here, then, our greatest deviation in weight and chest girth.

There seems no especial difference in the height of these individuals as compared to the other diabetics. Probably the somewhat shorter trunk length of the women is of no special significance since the men do not exhibit such difference. In these under weight groups, the weight predicted from chest girth is very close to the observed weight especially for the men. The weight predicted from trunk length is, for both men and women, about 10 kg. greater than the observed weight. Thus the Dreyer prediction reflects the condition of these patients so that the ratio of observed weight to Dreyer's standard weight is not far different here from that in other groupings of tables 1 and 2. For this ratio, the women have 87 and the men 91 per cent., but when comparison is made of the observed weight with the actuarial standards, the difference between these under weight groups and the other diabetic groups is shown more clearly since the women have a ratio of observed weight to actuarial weight of 71 per cent. and the men, 80 per cent. These are by far the lowest of such ratios which are exhibited in our tables. It is noteworthy that our so-called underweight group at the time of measurement shows an average loss from maximum weight of 22 per cent. for women and 15 per cent for men. These are roughly much the same percentages of weight loss which are found for other groupings of the patients. Since, however, they have a much smaller chest girth than the other groups, it is probably incorrect to compare them with actuarial standards. With the men, the Dreyer weight prediction from chest girth is 51.7 kg. but prior to diabetes, the average maximum weight of these men was 61.2 kg. With women the weight prediction from chest girth is 44.0 kg. with average maximum weight of 53.7 kg. Thus the chest girth at the time of measurement would indi-

cate a normal body-weight of about 9.5 kg. less than these patients report as their maximum body-weight. If the chest girth prediction of 51.7 kg. is normal for these men, then 61.2 kg. represents 118 per cent.; in like manner, if 44.0 kg. is normal for the women, then 53.7 kg. represents 122 per cent. In general, our data show that the chest girth changes with changes in weight, particularly as the individual tends to become obese, while for changes in the direction of emaciation, the chest girth does not shrink proportionately.* The chest measurements in these so-called under weight men and women are therefore at the time of measurement of course somewhat reduced and represent more truly the bony circumference. But it appears likely that at the time these people were at their maximum, they were really somewhat over weight when due consideration is made for their natural build as represented in their skeletal dimensions. It is questionable whether we have any individuals among the cases measured who have diabetes without a previous history of an over weight period. In any case their maximum weight occurred very near the onset of the diabetes mellitus.

Conclusion

About 27 per cent. of the patients whom we measured, according to actuarial standards, have never, even at maximum weight, been more than 5 per cent. overweight. But compared with the Dreyer standard these men average 8 per cent. and the women 11 per cent. over weight. These patients lost but little less in percentage of body-weight than the average for the whole group of men and women, respectively. Their observed weights show the lowest average of any diabetic group studied by us. These individuals exhibit also the smallest chest circumferences and are to be differentiated as of unusually slim build, hence our present standards do not accurately apply to them.

Carbohydrate tolerance

The women exhibit a considerably less carbohydrate tolerance than is found on the average for the men, consequently

* It is possible that the change in weight has been too rapid for the chest girth to follow.

the dividing line for producing two groups of each sex of approximately the same size had to be differently located, 1.5 gm. per kilogram being used for the men and 0.8 gm. per kilogram for the women. There are 38 men who show a carbohydrate tolerance of 1.5 gm. or less per kilogram of body-weight and 39 men who show more than this. The averages for the two male groups are 0.9 and 2.5 gm. Those with the lesser tolerance are, in general, the older men. They have lost more weight than the others by 5 per cent., but both groups of men have apparently been about the same amount over weight. The women show similar results. Those with a tolerance of 0.8 gm. or less per kilogram have lost on the average 28 per cent. from maximum weight as compared with a loss of 20 per cent. for the women with a tolerance of more than 0.8 gm. per kilogram. The women with the less tolerance have considerably less body-weight, nearly 4 kg., although curiously as with the men, they are slightly taller and have slightly longer trunks than the individuals with the greater tolerance. They also have smaller chests. While the average age of both groups of women is the same, 47 years, one group shows an average tolerance of 0.5 and the other of 1.7 gm. carbohydrate per kg. of body-weight.

The variations in carbohydrate tolerance between the different groups are found also in glucose tolerance but are found also in glucose tolerance but are less in degree. In fact the glucose tolerance appears quite constant. The contrast between the two methods of stating tolerance is clearly brought out by comparing the percentage variability for both series of measures on each sex separately. Thus the 77 men with an average carbohydrate tolerance of 1.7 gm. have a coefficient of variability of 48 per cent., while for glucose tolerance the average is 2.6 gm. and the coefficient of variability is 31 per cent. Similarly the 56 women have an average carbohydrate tolerance of 1.1 gm. and a coefficient of variability of 57 per cent., with a total glucose tolerance of 1.9 gm. per kilogram and a coefficient of variability of 33 per cent. Our data indicate that diabetic patients are therefore much more alike in glucose than in carbohydrate tolerance and that the latter is more significant in defining the actual condition of the patient when comparing him with other patients or with himself at different dates.

Conclusions

The carbohydrate tolerance per kilogram of body-weight for the patients measured is roughly one-third less with the women than with the men. Considering each sex separately, the individuals with the less carbohydrate tolerance show also smaller observed body-weights in spite of the fact that their stature is somewhat larger and therefore a greater body-weight would be expected. Apparently the amount of obesity which has existed has but little relation to the carbohydrate tolerance found at the time of measurement, but those who have had the smaller tolerance, have lost a greater percentage of what was at one time their maximum weight.

Obesity

In the previous discussion the factor which has continually been prominent is that of obesity. As a means to a better understanding of the influence of this factor, both sex groups of diabetics have been classified on this basis alone as given in table III.

Thus 15 per cent. above normal actuarial weight has been made the dividing line for both sexes, and those with a body-weight above this will for convenience be termed "obese", while those who reach this line or are below will be called "normal". The groups as thus divided as of approximately equal size.

From Table III it is seen that the obese are older by several years, have had the longer duration since onset, and a slightly lower carbohydrate tolerance in terms of body-weight. They show no marked deviation in height, trunk length, or ratio of trunk length to height, but have much larger chest circumferences. The obese men and women give observed weights 13 and 17 kg. higher than their respective comparison groups. It is noteworthy that the obese men have an average weight predicted from chest girth of 79.2 kg. as compared with observed present weight of 66.6 kg., notwithstanding the fact that they have lost 23.8 per cent. of their one time maximum weight (87.5 kg.) and that they are now weighing 97.9 per cent. of standard actuarial weight. The obese women show almost an exact parallel to this and moreover, their present

TABLE III.

The physical measurements of diabetic patients classified with reference to obesity prior to onset.

Diabetic Patients Average measurements and comparisons	RATIO MAX. WT. TO ACTUARIAL WT.			
	Men 115% and under	Men over 115%	Women 115% and under	Women over 115%
Total No. of cases	34	43	28	26
Average age	34	47	43	52
Duration of diabetes	4.2	5.8	2.8	5.2
Date of max. weight	1917	1913	1915	1913
Carb. tolerance, gm	99	110	57	68
Tolerance per kg. of wt	1.8	1.7	1.2	1.0
Glucose tolerance per kg.	2.8	2.5	1.9	2.0
Height, net in cm.	1716	170.2	159.4	159.3
Trunk (Dreyer) in cm.	88.9	89.0	84.2	85.0
Ratio: trunk to height	51.7	52.2	52.7	53.3
Chest circum. (Dreyer) cm.	81.4	92.3	70.7	81.3
Predicted chest from trunk	84.8	84.9	72.9	74.0
Observed net weight kg.	53.7	66.6	45.3	62.3
Predicted weight from chest	55.7	79.2	49.1	82.0
Predicted wt. from trunk	62.7	62.4	55 0	56.5
Dreyers' standard wt.	59.2	77.2	52.0	69.3
Actuarial standard wt.	65.9	67.9	60.2	62.8
Ratio: obs.wt. to Dreyer wt.	90.4	94.0	87.5	88.9
Ratio: obs. wt. to Actu'l.wt.	81.6	97.9	76.0	99.6
Maximum reported wt.	66.2	87.5	59.5	82.8
Ratio obs. wt. to max. wt.	82.1	76.2	76.5	74.6
Loss from max. wt. p. ct.	17.9	23.8	23.5	25.4
Actu'l. wt. at date of max.	64.4	66.3	58.5	60.7
Ratio: max.wt. to Actu'l.wt.	101.6	131.9	100 9	137.8

1 Medico-Actuarial standard.

weight predicted from chest is practically identical with their reported maximum. These facts certainly indicate that the obesity has left the chest in an enlarged condition. This question of skeletal change during and following obesity is surely of considerable importance and needs investigation by radiographic methods. Even the men and women who are "115 or under" have predicted weights from chest girth which are greater than the observed body-weights. The obese men and women show ratios of maximum weight to actuarial weight of 131.9 and 137.8 as compared with averages of about 100 for the less over weight groups.

Conclusion.

While obesity seems closely related to the onset of diabetes

mellitus, the intensity of the disease is not proportional to the amount of excess fat. Patients who before onset had the greater obesity also have had the greater duration.

PHYSICAL FITNESS OF DIABETIC PATIENTS

The term "physical fitness" at present has no distinctive meaning. It may refer to (1) good tissue development and nutritional state; (2) trained muscles capable of prolonged or vigorous performance; or (3) resisance to infections and the wear and tear of life. These various phases are not wholly independent of each other but at present there is no accepted comprehensive measurement scale or set of comparison standards against which we may assess the real physical fitness of an individual.

Body-weight

If considered over a long period, body-weight is undoubtedly an index of the nutritional state, and when taken in comparison with the weights of other individuals indicates something of the tissue development.

Diabetes is a disease in which the change in body-weight is a conspicuous symptom. Judging from our data, average diabetic subjects seen at the clinic have body-weights from 9 to 12 per cent. below the actuarial standard and 8 to 11 per cent. below Dreyer's standard, or in round numbers about 10 per cent. below normal. A few extreme cases are 20 to 30 per cent or even more below normal standards. A 10 per cent deviation from normal weight in the case of an individual is not significant. But when such a decrement occurs as an average for a group, and when no selection has been made in reference to height, body circumference, or other features, an observed weight 10 per cent below available normals indicates clearly a pathological condition or else the influence of some temporary factors. But with our subjects the amount of weight loss below normal does not represent gross change which has taken place. Actually these people have been on the average considerably overweight and have lost not 10 per cent but something over 20 per cent of the weight they once had. They show more emaciation than the group of

young men studied in an earlier investigation who had lived on a reduced diet for several weeks and had lost as a consequence of this regime approximately 10 to 12 per cent of their body-weight[11]. Therefore the comparison of observed body-weight with normal standards gives a definite indication that diabetic subjects as a group are not physically normal, and provides a statement for the degree of abnormality.

Vital capacity

The vital capacity could not be conveniently obtained for all of our subjects but trustworthy results were secured on 33 men and 35 women. These have been averaged for the various groups of patients as they were classified according to age, duration of diabetes, etc., and appear in tables 1 and 2 as item 28. As expected, the men have a higher vital capacity than the women, or 3,990 as compared with 2,336 cc. The younger patients, both men and women, give somewhat higher results than the older groups, also those with a duration of diabetes of two years or less. The patients who have lost 21 per cent or less in body-weight show a greater vital capacity by a small amount than those who have lost over 21 per cent. The men with the higher carbohydrate tolerance show the larger vital capacity but this is not found to be the case with the women.

For each man and woman on whom vital capacity measurements were secured, the Dreyer predictions for vital capacity on the basis of trunk length, chest girth, and observed weight were tabulated, each under the three classes, A, B, and C, which according to Dreyer, represent the different degrees of physical fitness. * Thus 9 prediction values were obtained of each patient. These have been averaged separately for men and women and the results given in table IV. As mentioned previously, the 33 men show an average vital capacity of 3990 cc. This is above their predicted vital capacity for class B, as calculated from trunk, chest, and weight and is also above class A for weight. Probably since body-weight and chest girth changes are prominent in diabetes it is most

* The three classes may be approximately indicated as follows: A — army and navy personnel, police force, athletes; B — professoinal classes, business and railway men; C — tailors, printers, clerks and factory workers.

TABLE IV.

The observed vital capacity of diabetic men and women compared with Dreyer's standards.

Diabetics		Dreyer's standard vital capacity for different classes of subjects								
Number sex	Observed vital capacity	Predicted from trunk			Predicted from chest			Predicted from weight		
		A	B	C	A	B	C	A	B	C
	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.	c. c.
33 men	3990	4137	3778	.....	4210	3850	.....	3754	3430	.....
35 women	2336	.....	2976	2785	.....	3043	2817	.....	2783	2603

1 Class "A" represents such individuals as army and navy personnel, athletes and out-door sportsmen, policemen and blacksmiths; Class "B", professional, business and railway men; and Class "C", tailors, shoemakers, printers and the usual factory workman. A somewhat similar grouping applies to women but relatively more of this sex are found in Class "C".

logical to compare the vital capacity on the basis of prediction from trunk length. On this basis the observed vital capacity stands about midway between class A and class B which places them midway between the out-door workers and the average for professional classes, railway men, clerks.

The 35 women with an average of 2,336 cc., show quite a different result. This average is distinctly below the prediction for these women on the basis of trunk length, chest girth, and even of weight. Their actual average is approximately as much below class C as B is above, so they may be designated as class D. The women whom we have measured had a more severe diabetes than the men of the series, but we have no way at present to judge whether this difference in severity is sufficient to account for the fact that the women show a vital capacity of class D while the men are in class B+. It is more difficult to secure vital capacity measures with middle-aged or elderly women than with men as they less readily exert themselves in performing the test. Our women, as a group, average 6 years older than the men and we have seen from the data in tables I and II that the older individuals show smaller vital capacity. The results as they stand for the women approximately correspond with the clinical picture for the physical condition and fitness of these patients and if we had no other results, could probably be taken to indicate that physical fitness may be well measured by vital capacity as has been urged by Dreyer. On the other hand, the data

for the women are probably less trustworthy than those for the men and these latter show that the vital capacity measurement itself is a very misleading index of physical fitness for diabetic patients. Thus, patient No. 1963, a woman, had a vital capacity of Class B+ on the basis of trunk length but this patient was a most severe diabetic, hardly strong enough to stand at the time of the measurement and died shortly afterward of diabetes and inanition.

CRITIQUE OF MEASUREMENTS

This investigation was begun with the sole objective of better understanding the physical condition associated with diabetes and with the hope of gaining some suggestions as to methods of classification and perhaps the treatment of such patients. The physical measurements which we have applied are few in number and probably not very well chosen. They were easily undertaken in connection with the routine examination of patients as they came to the hospital. We have made no anthropometric survey of diabetic patients, but this may be considered as a preliminary study which has yielded some observations that have a bearing on the whole scheme of physical measurements so far as these are taken in reference to normality of body-weight. Schemes of measurement are usually tested and "standardized" on normal material

TABLE V.

Relationship between certain of the physical measurements represented by correlation coefficients.

Pairs of measurements for which the correlation was determined	Diabetic men		Diabetic women	
	r	P. e	r	P.
Weight and chest girth	+.94	±.009	+.82	±.030
Weight and trunk [Dreyer]	+.45	±.061	+.53	±.065
Weight and height	+.35	±.067	+.09	±.089
Chest girth and trunk	+.34	±.068	+.10	±.089
Chest girth and height	+.21	±.074	—.04	±.090
Vital capacity and chest girth	+.16	±.114	—.21	±.109
Vital capacity and surface area	+.49	±.089	+.24	±.107
Vital capacity and trunk	+.74	±.053	+.60	±.073
Vital capacity and height	+.72	±.056	+.65	±.066
Vital capacity and weight	+.33	±.090	+.05	±.114

and then applied without special adjustment to pathological material. This method probably has a number of pitfalls.

To show the relationship existing between certain of the physical measurements obtained, we have worked out a number of correlation coefficients using Pearson's Products-Moments method, well known as the most satisfactory means of relating two series of measurements[12]. The various measurements between which correlations were determined, the correlation coefficients and probable errors for diabetic men and women are grouped in table V. A correlation coefficient of +1.00 indicate positive and complete interdependence while +0.00 means no relationship between the two characters as measured. Correlation coefficients to have much significance should be five or more times as large as their probable errors.

Predicting weight from chest circumference.

Attention is particularly called to our correlation figures in table 5, between observed weight and chest girth. These are +.94 and +.82 for men and women. In both instances the probable error is very small, indeed, the smallest in the table, as the correlations are the highest. As high correlation between biological characters is seldom observed. The close relation between body-weight and chest girth has always been popularly recognized but has found little notice in medical literature. High correlation figures have been published by others. Baldwin[13] found for groups of children 7 to 17 years old an average coefficient of +.86 for boys and +.89 for girls. He says "Between the yearly measurements of weight and the girth of the chest, the correlations are higher than for weight and any other physical trait measured". Davenport and Love[14] find +.69 +.001 for white and colored troops at mobilization and Gray[15] reports +.88 +.017 from 80 carefully measured healthy men ranging in age from 18 to 71 years. It is seen from this that our correlation figures for weight and chest girth obtained on pathological material agree very well with those obtained on supposedly normal material. All of these figures taken together demonstrate a very high degree of inter dependence between these two physical measurements. This being the case if we wish to know the normal weight for a given individual, it is theoretically incorrect to follow

Bornhardt, 1886 and 1887, Gray, 1917 and later, or Dreyer, 1920, in the principle which each has applied in somewhat different ways, namely, to measure the chest circumference and predict the normal weight from that, for to measure one is to measure the other, and we are only led in a circle. * A fat man makes for himself a high normal, while a lean man of the same stature makes a low one. (See Tables I and II). As these writers have urged, we undoubtedly need some measure or measures for the width of the body, but our belief is that these should be bony diameters, not circumferences, if they are to be the basis for weight prediction. Probably weight predictions from one or more skeletal diameters coupled with Dreyer's predicted weight from trunk, and possibly prediction from some other body length measure, all taken in combination will give the best basis for determining normal weight. The present situation is that Dreyer's weight standards, if the chest girth is used, are poorest when applied to obese subjects, and this is unfortunate since, with adults, it is more dangerous to be obese than to be thin. The Actuarial standards are also too lenient, as they allow considerable increase in weight with increasing age, and it is very doubtful whether this is physiological.

Vital capacity

The vital capacity demonstrates a fairly high degree of relationship with stem length in our series. The correlation for men is +.74 +.053 and for women +.60 +.073. Practically the same results are found with the heights, and both length factors correlate with vital capacity considerably more strongly than does surface area determined by the DuBois linear formula. The relationship with chest girth and with weight are apparently but slight, so that our pathological data are again in disagreement with Dreyer[16], who found vital capacity most closely related to weight in normal subjects.

Trunk length

The trunk length (Dreyer), or the more usual sitting height of the anthropologist[17], is about as near a bony skeletal

* DuBois and DuBois, Arch. Int. Med., 1916, Vol. 17, p. 863, found that height and weight serve about as well for calculating surface area as did their more elaborate scheme of heights and circumferences.

measurement as is stature, and has the same order of low percentage variability. (See Tables I and II). There is some current discussion as to whether one measure has any advantage over the other. In table V there are listed six correlations (three for men and three for women) of the trunk length with other physical factors. Height has likewise been correlated with these same factors and in five instances the trunk correlations are higher than those with height, *i. e.,* total stature. Judged on this basis, the trunk measurement is the more useful, as it seems to include the vital part of body length.

CONCLUSIONS

1. A group of 133 diabetic men and women have been compared with both Dreyer's and the Medico-Acturial weight standards. Altho normal in stature, they are found to have been on the average 20 per cent over-weight prior to onset, and at the time of examination are about ten per cent under weight.

2. The 56 women showed more severe diabetes than the 77 men, and as a class had much lower tolerance per kilogram of body weight, whether expressed as total available glucose, or as the carbohydrate, in the diet.

3. Glucose tolerance per kilogram of body weight is more uniform between different diabetic patients than is the carbohydrate tolerance. The latter appears, therefore, the more definitive expression for tolerance in diabetes.

4. The older diabetics have been more obese, have lost a larger percentage of their maximum weight, and demonstrate the longer durations .

5. Diabetics who have never been obese according to Medico-Actuarial standards are found to have been 10 per cent over weight when compared with Dreyer's standard. They are distinguished by abnormally narrow chests and probably have been fat for their build.

6. Obesity is closely related to the onset of diabetes mellitus, in fact, almost invariably present, but the intensity of the disease frequently appears inversely proportional to the amount of excess fat.

7. Obesity produces an anatomically enlarged chest girth,

which does not entirely return to normal after the excess weight is lost.

8. Chest circumference is closely dependent on body weight and reflects temporary weight variations, especially in the obese. It should not be used as a measure for predicting the normal weight. We advise investigation of the feasibility of substituting some bony diameters for use in predicting weight.

9. The average diabetic patient is not physically fit, using body weight as an index. His vital capacity may be as large as that of normal individuals, notwithstanding his bodily weakness. Vital capacity measurements in uncomplicated diabetes are not clinically helpful.

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EXPERIMENTAL STUDIES IN DIABETES

Series IV. Lipemia. 1. Analyses of blood lipoids in diabetic animals and patients.

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The following incomplete experimental observations are published for such information as they may contribute to the problem of lipemia. The methods of Bloor[1], which were used for all analyses, are sufficiently well known to require no description. The writer is indebted to Professor Bloor for personal instruction in some details of the use of these methods, and for review of the results as finally tabulated. Under existing circumstances, it has not been possible to check and harmonize the analytical figures by allowances for personal and other variable factors, as was done by Gray[2] in his admirable studies in this same field. The only exception to this statement is found in the fact that though whole blood, plasma and corpuscles were regularly analyzed separately, calculated values were sometimes substituted for the analytical figures for the corpuscles when the latter were too discrepant. All blood samples were centrifuged promptly and treated immediately with alcohol-ether to avoid changes in standing, and other precautions used as recommended by Bloor.

Dog E5-88, an old mongrel with Welsh terrier blood, weighing 11.25 kg., was partially depancreatized Aug. 24, 1917. The tissue removed weighed 18.0 gm., and the remnant about the main duct was estimated at 1.6 gm. (1/12 — 1/13). Glycosuria followed, first on bread and then on protein-fat diets. While the dog was in use for other experiments, he displayed a moderate tendency to lipemia, as judged by occasional milky plasma. Nevertheless, the plasma was generally clear, and the animal seemed suitable for a trial of agents which might possibly give rise to lipemia. During the whole of October, the plasma remained clear on a diet of 300 gm. beef lung and

Table I.

Dog E5-88.

Date 1917	Time	Wt. Kg.	DIET		URINE			BLOOD				TOTAL FAT			Cholesterol			LECITHIN			Total Fatty Acid			Glycerides		TFA/C			TFA/L			L/C		
					Volume c.c.	Sugar gm.	Acetone qual.	Plasma Sugar mg per 100cc.	CO_2 vol. %	Lipemia qual.	Corp. vol. %	Total Acetone mg. per 100cc.	Wh. Blood %	Plasma %	Corp. %	Wh. Blood %	Plasma %	Corp. %	Wh. Blood %	Plasma %	Corp. %	Wh. Blood %	Plasma %	Corp. %	Plasma %	Corp. %	Wh. Blood	Plasma	Corp.	Wh. Blood	Plasma	Corp.	Wh. Blood	Plasma	Corp.
Oct. 31	8:30 pm.	—	300 gms. Lung	100 gms. Suet	280	0.56	Faint	476	55.7	Neg.	42.5	Neg.	—	—	—	0.24	0.20	0.30	—	0.16	—	—	—	—	—	—	—	—	—	—	0.80	—
	3:00 pm.							370	55.7	,,	36.2	,,	—	—	—	0.28	—	—	0.18	—	—	—	—	—	—	—	—	—	—	0.64	—	—
	4:14 pm.							345	56.7	,,	44.5	,,	—	—	—	0.20	0.21	0.18	0.19	0.19	0.19	—	—	—	—	—	—	—	—	0.95	0.90	1.06
Nov. 5	10:45 pm.	8.0	,,	,,	310	heavy	,,	238	64.3	,,	39.0	,,	—	—	—	0.29	0.23	0.39	0.21	0.37	0.17	—	—	—	—	—	—	—	—	0.72	1.60	0.43
,, 8	9:00 am.	—	,,	,,	450	9.45	Slight	370	61.3	,,	43.6	,,	0.89	—	—	0.29	0.23	0.29	—	0.22	—	0.60	—	—	—	—	2.07	—	—	—	—	0.76	—
	3:00 pm.							370	59.4	,,	37.4	,,	3.28	3.24	3.50	0.30	0.29	0.32	0.51	0.33	0.79	2.98	2.95	3.04	2.73	2.63	9.95	10.19	9.50	5.84	8.97	3.85	1.70	1.14	2.41
	5:00 pm.							435	61.7	,,	33.8	,,	2.57	—	—	0.26	0.28	0.23	0.18	0.21	0.14	2.31	—	—	—	—	8.90	—	—	12.83	—	—	0.69	0.75	0 61
,, 12	9:30 am.	—	,,	,,	280	3.02	Neg.	333	55.5	,,	32.5	7.4	1.78	1.75	1.84	0.37	0.37	0.39	0 38	0.50	0.10	1.41	1.38	1.48	0.92	1.48	3.81	3.73	3.80	3.71	2.76	14.80	1.03	1.35	0.26
	3:30 pm.							475	63.2	,,	34.6	Neg.	1.53	—	—	0.37	0.43	0.26	0.49	—	—	1.16	—	—	—	—	3.14	—	—	2.37	—	—	1.32	—	—
	5:30 pm.							400	59.4	,,	32.4	,,	0.84	1.78	—	0.37	0.37	0.38	0.69	0.49	1.06	0.47	1.41	—	0.98	—	1.27	3.81	—	—	2.87	—	1.87	1.32	2.79
,, 13	10:00 am.	—	,,	,,	383	4.38	Doubtful	270	47.7	Faint	37.0	Trace	1.52	—	—	0.32	0.36	0.25	0.33	0.32	0.35	1.20	—	—	—	—	3.75	—	—	3.64	—	—	1.03	0.88	1.40
	4:00 pm.							415	65.2	Mod.	34.7	,,	1.95	—	—	0.36	0.39	0.32	—	0.37	—	1.59	—	—	—	—	4.42	—	—	—	—	—	—	0.90	—
	6:00 pm.							312	55.7	Heavy	36.1	,,	2.80	3.20	1.83	0.36	0.38	0.32	—	0.47	—	2.44	2.82	1.51	2.34	—	6.78	7.42	4.72	—	6.00	—	—	1.23	—
,, 19	9:00 am.	8.6	,,	,,	370	1.45	V. Faint	475	47.0	Faint	42.3	5.4	1.90	—	—	—	0.23	—	0.40	0.33	0.48	—	—	—	—	—	—	—	—	—	—	—	1.43	—
	3:30 pm.							435	57.4	Slight	35.7	5.7	1.65	2.90	—	0.20	0.19	0.23	0.36	0.26	0.53	1.42	2.71	—	2.57	—	7.18	14.30	—	3.94	10.42	—	1.80	1.37	2.30
	5:00 pm.							455	57.4	,,	38.7	6.1	2.55	3.00	1.83	0.22	0.79	0.26	—	—	—	2.33	2.81	1.57	—	—	10.59	14.80	6.04	—	—	—	—	—	—
,, 20	10:30 am.	—	600 gms. Lung		340	6.46	,,	370	54.6	Doubtful	40.3	Neg.	0.94	0.99	0.87	0.19	0.16	0.24	0.14	0.26	—	0.75	0.83	0.63	0.59	—	3.95	5.19	2.62	5.36	3.19	—	0.73	1.62	—
,, 26	9:45 am.	—	,,		420	8.99	,,	286	57.6	Faint	34.5	Trace	—	1.82	—	0.20	0.20	0.20	0.18	0.16	0.21	—	1.62	—	1.43	—	—	8.10	—	—	10.12	—	0.90	0.80	1.05
	3:45 pm.							500	61.4	,,	42.9	,,	0.85	1.18	0.38	0.20	0.21	0.19	0.23	0.15	0.33	0.65	0.99	—	0.86	—	3.25	4.71	—	2.83	6.60	—	1.15	0.71	1.74
	5:45 pm.							525	67.2	,,	41.5	,,	0.93	0.97	0.87	0.21	0.25	0.14	0.20	0.17	0.24	0.72	0.72	0.72	0.53	0.59	3.43	2.93	5.14	3.60	4.23	3.00	0.95	0.68	1.71
Dec. 1	10:00 am.	7.0	,,		650	11.70	,,	303	59.5	Slight	44.7	11.3	—	0.82	—	0.22	0.18	0.27	0.28	0.19	0.32	—	0.64	—	0.44	—	—	3.56	—	—	3.37	—	1.27	1.05	1.19
	4:00 pm.							435	77.7	Neg.	38.0	—	1.45	1.78	0.79	0.21	0.18	0.26	0.23	0.18	0.32	1.24	1.60	0.53	1.47	0.33	5.90	8.90	2.04	5.39	8.89	1.66	1.10	1.00	1.22
	6:00 pm.							333	68.1	,,	41.0	—	—	1.96	—	0.24	0.19	0.32	0.29	0.11	0.50	—	1.77	—	1.13	—	—	9.37	—	—	16.09	—	1.26	0.58	1.56
,, 5	9:30 am.	—	,,		580	14.50	,,	435	59.5	Faint	41.1	Neg.	1.98	—	—	0.24	0.12	0.41	—	0.20	—	1.74	—	—	—	—	7·25	—	—	—	1.66	—			
	4:00 pm.							525	55.7	,,	38.7	,,	—	1.73	—	0.17	0.18	0.15	0.30	0.11	0.57	—	1.55	—	1.47	—	—	8.61	—	—	14.09	—	1.76	0.61	0.38

Oct. 31.—Fed diet immediately after first blood sample.
Nov. 5.—1 gm. cholesterol added to diet.
Nov. 8.—Fed immediately after first bleeding.
Nov. 13.— " " " " "
Nov. 12.— " " " " "

Nov. 19.—Fed immediately after first bleeding.
Nov. 20.—Cholesterol stopped.
Nov. 26.—Fed immediately after first bleeding.
Dec. 1.—1 gm. cholesterol added to diet of Nov. 22.
Dec. 5.—5 gm. lecithin added to diet of Dec. 2.

100 gm. suet. Some of the analyses performed on Oct. 31 were saved. The plasma remained clear, but an apparent abnormality may be found in the failure of lecithin to increase during digestion. The cholesterol in the plasma remained practically unchanged. The meaning of the considerable fall of cholesterol in the corpuscles is not understood.

Similarly incomplete figures exist for a single blood sample taken before feeding on Nov. 5. With increase of the glycosuria and the severity of the diabetes, there was an increase of cholesterol in both plasma and corpuscles and also an increase of lecithin in the plasma, as compared with Oct. 31. On the other hand the lecithin of the corpuscles was lower rather than higher, as frequently noticed in diabetic lipemia. Notwithstanding these changes in lipoids, the plasma still was clear. Beginning on this day, 1 gm. of pure cholesterol was added to the daily diet.

Nov. 8, analyses were performed in order to learn the effect of this diet. The figures for total fat and fatty acids in whole blood suffice to show that a masked lipemia was present, not betraying itself by any appreciable turbidity of the plasma. The rise and fall of the curve indicate active fat absorption, but yet the duration as well as the height of the curve is abnormal. Cholesterol in the plasma remained unchanged, but in the corpuscles rose at the height of lipemia (3:00 P. M.) and then fell with the decline of lipemia. Lecithin rose to a surprising degree in the plasma and especially in the corpuscles at the height of the lipemia, then fell sharply with the decline of the lipemia. The ratios between total fatty acids, lecithin and cholesterol showed corresponding changes. The outstanding feature is the disproportionate increase of fatty acids in the form of neutral fat, so that the ratios of this to lecithin and cholesterol are excessive. Though such high ratios seem to be characteristic of all severe forms of lipemia, they were found in this case at a stage when the plasma was not yet milky.

On Nov. 12, the total fat and fatty acids in both corpuscles and plasma were abnormally high before feeding, and fell during the usual digestive period. Both the initial height and the fall can be explained hypothetically by delayed digestion and absorption. The cholesterol was higher than before, but the rise in the plasma and fall in the corpuscles at 3:30 P. M.

are not explainable. The lecithin was at a high level throughout; it failed to increase in the plasma, but increased remarkably in the corpuscles. The single exception to this statement is found in the low corpuscle lecithin (0.1%) before feeding, which also is responsible for the unusually high ratio of total fatty acids to lecithin; but as this analysis is so decidedly out of series it may be incorrrect. On the whole, the ratios of fatty acids to both cholesterol and lecithin were lower than before.

The same experiment was repeated on the following day, when for some reason the digestive function seemed to be strikingly better. The visible lipemia was the heaviest seen at any time in this dog. The total fat and fatty acids increased during the 8 hours of observation, though the incomplete analyses give the impression that this increase was in the plasma rather than in the corpuscles. The cholesterol increased slightly in both plasma and corpuscles. The increase of lecithin in the plasma was more marked, but figures for the corpuscles are not available. The ratios of total fatty acids to lecithin and cholesterol were high, as usual in heavy lipemia. The ratios between cholesterol and lecithin were not notably different from those on other days. In general, neither the absolute nor the relative values for any of the lipoids furnish any explantion of the milky or creamy appearance of the plasma, due to free fat, in contrast to the clear plasma of the previous days. In particular, on Nov. 8 the total fat in whole blood and plasma reached higher figures than on Nov. 13, without appreciable turbidity. The only possible clue may perhaps be found in the higher concentration of fat in the corpuscles on the former as compared with the latter date.

Nov. 19, the lipemia was lower than on Nov. 13, though the gross appearance of the plasma had changed somewhat more than the chemical analyses. The ratios of total fatty acids to both lecithin and cholesterol were higher than before, also the ratios of lecithin to cholesterol were slightly higher. At this time the fatty diet had raised the dog's weight to the highest level seen during this experimental period, namely 8.6 kg.

By the morning of Nov. 20, all the lipoid analyses had fallen decidedly and the plasma was practically clear in appearance.

On this day both suet and cholesterol were discontinued, and the diet was changed to 600 gm. of lung only. On this diet the glycosuria increased, and the body weight fell by Dec. 1 to 7 kg. Beginning Nov. 22, 1 gm. of pure cholesterol was added daily to this low-fat diet.

Nov. 26, analyses were performed for the 8 hours following the giving of this diet. The total fat and fatty acids steadily diminished in the plasma, but an increase occurred in the corpuscles, at least for the period from 3:45 to 5:45 P. M. Cholesterol increased slightly in the plasma but fell in the corpuscles. Lecithin remained constant in the plasma but increased in the corpuscles. The ratios of total fatty acids to cholesterol and lecithin remained high. The ratios of cholesterol to lecithin were within the ordinary limits.

Dec. 1, on the same diet, the total fat and fatty acids started at a lower level than before but increased during digestion in the plasma. The single analyses for 4 P. M. indicated comparatively small quantities in the corpuscles. Lecithin started at a higher level than on any other day of the fat-poor diet, and decreased considerably in the plasma during digestion. In the corpuscles it remained stationary in the earlier part of this period, but in the later stage it increased greatly. The ratios of total fatty acids to cholesterol and lecithin increased, as usual, with the increase of lipemia. The ratio of lecithin to cholesterol fell in the plasma but rose in the corpuscles.

Beginning Dec. 2, in addition to the 1 gm. of cholesterol the dog was given 5 gm. of lecithin with the diet. Dec. 5, partial analyses were obtained of two blood samples, namely at 9:30 A. M. before feeding, and at 4 P. M. The total fat and fatty acids started at a high level, but showed no increase, as far as can be judged by comparison of the figures for whole blood in the morning and for plasma in the afternoon. There was a considerable rise of cholesterol in the plasma and a still greater fall in the corpuscles. Lecithin diminished in the plasma, but a rise in the corpuscles may be assumed with probability, from the high figure at 4 P. M. The ratios between the different lipoids showed no instructive variations.

In summary, any changes attributable to the addition of cholesterol or lecithin to the diet were slight and not always regular. Neither of these substances showed any great tendency to accumulate in the blood, or to cause any striking increase

of the lipemic tendency. Visible lipemia, as opposed to the "occult" fat in the clear plasma, was not determined by the absolute quantities of fatty bodies present or by any distinct change in their proportions to one another. Also, there was no evident parallelism between the lipemic tendency and either the sugar or the acetone bodies in urine or blood.

Dog E5-08, a brindle female mongrel aged 3 years and weighing 10.6 kg., was partially depancreatized March 17, 1917. The tissue removed weighed 24.2 gm. The remnant about the main duct was estimated at 2.8 gm. (1/9 — 1/10). Up to April 9, various diets of carbohydrate, protein and fat caused heavy glycosuria, which was checked by intervals of fasting or low diet. April 9 to 13, only 100 gm. of suet was fed daily, and glycosuria ceased. April 13 to May 1, diets of 800 to 400 gm. lung with 100 gm. suet daily caused heavy glycosuria with no more than traces of acetone. The body weight had gradually fallen below 9 kg. May 1 to 23, experiments were performed as shown in Table II.

May 2, blood analyses were done before and after feeding the lung and suet diet. The 6 P. M. blood sample, taken approximately 6 hours after the meal, showed a gross appearance of marked lipemia. Curiously, the total fat found by analysis in the plasma was slightly lower instead of higher, as compared with the fasting blood. The increase of fat in the whole blood was due to the very great increase of corpuscle fat. After feeding, cholesterol was decreased and lecithin increased in both plasma and corpuscles. The ratio of total fatty acids to cholesterol rose after feeding in both whole blood and plasma. The ratio of total fatty acids to lecithin rose slightly in the whole blood and fell markedly in the plasma. The ratio of lecithin to cholesterol rose in both plasma and corpuscles.

On May 3, only 100 gm. of suet was fed, in the attempt to increase both lipemia and acidosis.

May 4, the dog was given a lipoid-rich meal in the form of 500 gm. of beef brains, and only faint appearances of lipemia were shown grossly in the blood samples taken 4 and 8 hours later. The total fat increased in the plasma but decreased in the corpuscles; but the plasma in no instance contained as much fat as on May 2, when lipemia was plainly visible. Cholesterol increased markedly in the corpuscles but di-

minished slightly in the plasma. Lecithin rose slightly in both corpuscles and plasma. It was evident that the increase of fatty acids in the plasma was chiefly in the form of glycerides. The ratio of total fatty acids to both cholesterol and lecithin fell in the whole blood but rose markedly in the plasma. The ratio of lecithin to cholesterol first rose and then fell in the whole blood, and rose in the plasma.

A diet of 500 gm. lung and 100 gm. suet was continued through May 10. The appearance of qualitative lipemia failed to increase, and the analytical results were equally negative. Neither total fat, cholesterol nor lecithin showed any regular or important rise in either plasma or corpuscles.

Intravenous injections of sodium carbonate were given on May 9, and of hydrochloric acid on May 10, as shown in the table. Only the analyses for cholesterol and lecithin are available, and these showed no important changes.

May 11 to 15, the diet was composed of beef lung, bread and suet, with addition of lard on May 13. The protein and carbohydrate were given partly to increase glycosuria and partly to enable the dog to digest as large quantities of fat as possible. Visible lipemia did not result. Only partial analyses for lecithin and cholesterol were saved. Both of these lipoids diminished in the plasma during digestion on May 15, but increased in the corpuscles.

May 16 to 23, the diet of lung, suet and bread was increased with a lipoid-rich material, namely 240 gm. of egg yolk. On the first of these days, intravenous injections of sodium bicarbonate were given as shown in the table. A slight opacity appeared in the plasma, corresponding to an increase of total fat during digestion. Cholesterol rose markedly in the plasma but fell in the corpuscles, so that a fall ocurred in the whole blood. Lecithin likewise increased in the plasma but decreased in the corpuscles, in such manner that the values in whole blood remained constant. There was a general rise of the ratios of total fatty acids to both lecithin and cholesterol, while the ratios of lecithin to cholesterol underwent no significant change.

May 17, this same diet without intravenous injections produced gross appearances of heavy lipemia and the highest total fat analyses of the entire experiment. Here cholesterol failed to rise in the plasma, but increased markedly in the

corpuscles and whole blood. The behavior of lecithin seemed peculiar, in that it first rose in the plasma and fell in the corpuscles (2 P. M.), and then fell in the plasma and rose in the corpuscles, so that the figures for the whole blood scarcely changed. As this was the heaviest lipemia, so also the ratios of total fatty acids to cholesterol and lecithin were the highest of the series. The ratios of lecithin to cholesterol fell with the rise of lipemia.

May 18 and 19, the same diet was given, followed with 5 gm. sodium bicarbonate by stomach tube. The plasma remained clear during the digestive period. The fasting level of blood fat was above normal, but it failed to rise after feeding. Nothing special can be said concerning the behavior of cholesterol and lecithin.

Administration of hydrochloric acid by stomach tube on May 20, 21 and 22 resulted in marked lowering of the CO_2 capacity of the plasma but no lipemia. The plasma remained clear in appearance, and no specific changes in the lipoids are shown in any of the analyses that were saved. At 1:15 P. M. on May 23 the dog was dyspneic, weak and apparently dying. Therefore a blood sample was taken, and 3 gm. sodium bicarbonate (60 cc. of 5% solution) was injected into a jugular vein. The CO_2 capacity of the plasma was thus raised, but the clinical condition was not improved and death occurred a few minutes later.

The decline of lipemia in the closing days of this experiment was probably due to weakness and impaired intestinal absorption. The observations apparently suffice, however, to exclude any marked alterations in blood lipoids due to alkali or acid administration and the associated changes in plasma bicarbonate.

Patient No. 24 was a man with severe diabetes, described in the previous clinical monograph[2]. Heavy lipemia, as judged by the creamy appearance of the plasma, was present at his first admission to hospital with active diabetic symptoms in November, 1914; but throughout his subsequent history, with glycosuria absent or very transitory, no more than a slight turbidity of the plasma was ever found. Following his third admission on June 25, 1917, a blood sample at 9 A. M. on June 26 (before breakfast) showed abnormally high values for both sugar (0.208%) and fat (3.88% in plasma with only faint

Table III.

Patient No. 24.

Date 1917	Hour	Diet				Plasma						Total Fat			Cholesterol			Lecithin			L/C	
		Protein gm.	Fat gm.	CH gm.	Cal.	Sugar Mg per 100cc.	CO_2 vol. %	Qual Acetone	Acetone + diacetic acid, mg. per 100cc.	B-oxybutyric acid, mg. per 100cc.	Total Acetone mg. per 100cc.	Qual. lipemia	Wh. Blood %	Plasma %	Corp. %	Wh. Blood %	Plasma %	Corp. %	Wh. Blood %	Plasma %	Corp. %	Plasma	Corp. %
June 26	9:00 a.m.	75	167	7	1902	208	59 8	Mod.	—	—	38 1	Faint	2 90	3 88	2 53	0 71	0 81	0 45	0 35	0 21	0 62	0 30	1 38
" 29	9:00 a.m.	75	267	7	2819	314	56 0	"	—	—	37 7	"	3 35	4 02	1 69	0 68	0 81	0 38	0 21	0 29	0 36	0 36	0 95
" 30	5:00 p.m.	75	267	7	2819	250	52 2	Heavy	—	—	52 3	Slight	—	3 88	—	0 59	0 74	0 30	0 28	0 25	0 34	0 34	1 11
July 1	11:00 a.m.	75	267	7	2819	320	52 2	Mod.	—	—	64 0	"	1 82	1 58	0 73	0 48	—	—	0 29	0 10	0 66	—	—
" 2	9:00 a.m.	75	13	7	451	303	61 7	—	—	—	72 0	Faint	—	3 25	—	0 51	0 08	0 17	0 21	0 19	0 26	0 28	1 47
" 9	9:00 a.m.	75	13	7	451	175	69 2	Faint	—	—	29 4	Neg.	2 03	2 76	0 45	0 48	0 83	—	0 19	0 15	0 30	0 18	—
" 13	9:00 a.m.	Fast	Day		—	238	69 2	"	—	—	22 3	"	1 97	2 44	1 13	0 77	0 84	0 64	0 21	0 21	0 22	0 25	0 38
" 22	10:00 a.m.	Fast	Day			111	—	Neg.	—	—	9 4	"	2 25	—	—	0 69	0 76	0 51	0 29	0 20	0 21	0 36	0 39
" 23	9:00 a.m.	75	13	7	451	98	55 1	"	—	—	18 5	"	—	2 00	—	0 43	0 66	0 30	0 18	0 22	0 11	0 33	0 37
" 28	5:30 p.m.	75	13	7	451	167	61 7	"	—	—	11 1	"	—	2 41	—	0 67	0 77	0 48	0 23	0 19	0 30	0 25	0 63
" 29	10:30 a.m.	Fast	Day		—	178	65 4	"	—	—	8 1	"	1 98	2 36	1 26	0 64	0 75	0 43	0 21	0 18	0 28	0 24	0 65
" 30	9:00 a.m.	75	13	7	Food 451 Alcohol 945 Total 1400	102	60 7	"	—	—	8 7	"	2 00	—	—	0 64	0 61	0 70	0 26	0 14	0 43	0 23	0 61
Aug. 4	5:15 p.m.	75	114	7	1398	222	73 0	Slight	—	—	36 8	Faint	3 02	3 00	3 09	0 58	0 73	0 26	0 37	0 35	0 40	0 48	1 54
" 5	10:00 a.m.	Fast	Day			217	76 8	"	—	—	21 2	Neg.	—	2 25	—	0 52	0 52	0 52	0 25	0 28	0 20	0 54	0 38
" 6	10:00 a.m.	75	168	7	1902	184	69 2	"	—	—	22 1	"	—	2 00	—	0 56	0 66	0 37	0 26	0 23	0 31	0 35	0 84
" 11	4:00 p.m.	75	233	7	2498	270	67 3	Heavy	23 0	35 0	58 0	"	—	2 75	—	0 61	0 58	0 68	0 26	0 23	0 32	0 40	0 47
" 12	9:00 a.m.	—	100	—	930	220	—	"	12 4	16 4	28 8	"	1 43	1 92	0 35	0 56	—	—	0 25	0 29	0 16	—	—
" 13	10:00 a.m.	75	233	7	2498	196	64 4	"	13 9	25 0	38 9	"	—	2 07	—	0 44	0 53	0 25	0 19	0 21	0 16	0 40	0 64
	5:00 p.m.	—	—	—	—	170	59 8	"	22 5	47 6	70 1	Mod.	—	2 80	—	0 59	0 66	0 44	0 33	0 22	0 53	0 33	1 44
" 14	9:00 a.m.	75	233	57	2498	270	62 3	"	19 5	26 6	44 1	Neg.	1 64	2 15	—	0 38	0 52	0 09	0 33	0 18	0 63	0 35	7 00
	5:00 p.m.	—	—	—	—	400	76 8	V.Hvy.	23 7	31 7	55 4	Slight	1 52	—	—	0 41	0 47	0 25	0 11	0 09	0 18	0 19	0 72
" 15	9:00 a.m.	75	233	7	2498	323	64 5	Heavy	14 5	15 1	29 6	"	1 62	1 98	0 79	0 50	0 49	0 51	0 33	0 26	0 57	0 53	1 12
	5:15 p.m.	—	—	—	—	294	—	V.Hvy.	21 4	32 8	54 2	Mod.	2 32	2 80	0 91	0 46	0 48	0 44	0 25	0 23	0 12	0 48	0 27
Sept. 2	11:00 a.m.	Fast	Day		—	182	—	Neg.	—	—	—	Neg.	—	2 00	—	0 64	0 66	0 60	0 17	0 14	0 22	0 21	0 37
" 3	9:00 a.m.	50	4	—	237	88	57 4	"	Neg.	38 6	38 6	"	1 53	2 21	0 43	0 48	0 75	0 51	0 24	0 18	0 31	0 21	0 61
" 10	9:00 a.m.	50	4	—	237	80	63 2	"	16 8	16 8	—	"	1 88	1 92	1 57	0 26	0 28	0 25	0 28	0 22	0 37	0 79	1 48
" 16	10:00 a.m.	1 3	0 5	6	33	89	54 8	"	—	—	—	"	0 96	—	—	0 39	0 69	—	0 20	0 21	0 18	0 30	—
" 22	5:00 p.m.	55	4	25	364	79	64 2	"	—	—	—	"	1 00	1 17	0 67	0 35	0 23	0 58	0 18	0 10	0 32	0 41	0 54
" 23	10:00 a.m.	13	3	30	199	76	66 2	"	—	—	—	"	1 04	1 27	0 51	0 34	0 33	0 35	0 14	0 10	0 12	0 49	0 34
" 24	10:00 a.m.	56	75	30	1045	67	72 0	"	—	—	—	"	1 04	1 26	0 71	0 49	0 31	0 76	0 21	0 07	0 42	0 23	0 55

July 2.—Cholesterol-free diet begun.
July 29.—Plasma still has a decided yellow color.
August 4.—This diet began July 31.
August 11.—This diet began Aug. 9.

August 12.—Given only 100gm. of olive oil.
August 14.—Given 50gm. levulose in addition to diet.
August 16.—Cholesterol-free, CH-free diet started.

visible turbidity), also a marked elevation of cholesterol (0.71% in whole blood, 0.81% in plasma). Lecithin was distinctly increased in the corpuscles (0.62%) but not in the plasma (0.24%). The CO_2 capacity of the plasma was normal at 59.8 volume per cent, but acidosis was indicated by a moderate nitroprusside reaction and total acetone of 38.1 mg. per 100 cc.

From June 29 to July 1, the allowance of 75 gm. protein and 7 gm. carbohydrate was increased by fat addition to more than 2800 calories, which represented a level far above the patient's known caloric tolerance. Accordingly, before breakfast on July 2 the plasma sugar was 0.303 %, the total acetone had risen to 72 gm. per 100 cc., and the urine contained considerable sugar and acetone; but the qualitative lipemia was still faint and the analyses for total fat and cholesterol were somewhat lower than on June 26. It thus appeared improbable that heavy lipemia could be restored, unless by means of a return of heavy glycosuria and other symptoms, which would be injurious to the patient.

Accordingly, on July 2 an opposite experiment was begun, in the form of an attempt to clear up the existing lipemia. The protein and carbohydrate allowance was left unchanged, but the fat was reduced to 13 gm., making the total diet 451 calories daily. This diet was also chosen so as to be as strictly cholesterol-free as possible. By July 9 this regime had reduced the plasma sugar to 175 and the plasma acetone to 29.4 mg. per 100 cc. Glycosuria had ceased and ketonuria was trivial. The plasma was clear in gross appearance, but still contained 2.76 % total fat and 0.83 % cholesterol. Both total fat and cholesterol were greatly reduced in the corpuscles. The lecithin had fallen to much lower figures in both plasma and corpuscles.

Except for 3 fast-days, the above diet was continued to July 30. From July 22 to 30 the plasma sugar before breakfast was normal. On July 28, hyperglycemia of 0.167 % was observed during digestion at 5:30 P. M., and on the fast-day of July 29 the figure of 0.178% is an example of the hyperglycemia which may follow a breakfast even when this consists of substances supposed to have no food value. Though the plasma was clear in gross appearance both fasting and during digestion, the total fat and cholesterol remained stubbornly

at high levels, very little influenced by the period of fat-poor and cholesterol-poor diet or the attendant improvement in sugar metabolism.

July 31 to Aug. 15, the allowance of 75 gm. protein and 7 gm. carbohydrate was maintained, but the calories were raised by large additions of cholesterol-free fats, which reached a maximum with 2198 total calories between Aug. 9 and 15. This increase of fat brought back high figures of sugar and acetone in the blood and caused glycosuria and ketonuria. The plasma mostly remained clear in samples before breakfast, and in samples during digestion the turbidity was only slight to moderate. The analyses for total fat rose only a trifle higher than on the preceding fat-poor diet, while the values for cholesterol actually fell, though not to a normal level. The values for lecithin fluctuated, as respects both different days and different periods of digestion, but on the whole were higher than on the fat-poor diet. The effect of the addition of 50 gm. of levulose to the diet on Aug. 14 was questionable.

After Aug. 15, the high fat diet was broken off, in order to prevent further harm to the patient from active diabetic symptoms. Accordingly, from Aug. 16 to Sept. 16, a more rigorous attempt to control the condition was made by means of a very low diet of only 50 gm. protein and 4 gm. fat, carbohydrate-free and cholesterol-free. After Sept. 3 the plasma sugar concentration was constantly below 0.09 %, and acetone was absent from blood and urine. By this means a marked fall was produced in all the blood lipoids, though the total fat was still generally above 1 % and the cholesterol values were mostly above normal.

The addition of 25 or 30 gm. of carbohydrate was tolerated without hyperglycemia, so that the fasting plasma sugar on Sept. 24, after the preceding low protein day, had fallen to a minimum of 0.067%. The lipemia was not further reduced by the carbohydrate; in fact, accidentally or otherwise, some of the analyses rose slightly.

Patient No. 43 was a young woman with very severe diabetes, whose history was given in the previous clinical monograph[4]. After she had been for a considerable time in the hospital at her third admission, and was free from active symptoms after a series of previous diet experiments, the present

observations were begun on a carbohydrate-free diet of 60 gm. protein and 253 gm. fat, making up 2597 calories daily. This diet was continued from May 22 to May 30, 1917, with a fast-day on May 27 on which only 30 gm. of olive oil was given. This excess of fat caused hyperglycemia and heavy glycosuria and ketonuria, as shown in the previously published record. The plasma of fasting blood samples was clear, but in samples during digestion there was slight to heavy turbidity. It is noticeable in Table IV that the analyses for total fat were decidedly above normal in both plasma and corpuscles, fasting and during digestion, but cholesterol and lecithin were lower than in patient No. 24. The ratios of total fatty acids to cholesterol and lecithin were high, as characteristic of any marked lipemia.

May 31 to June 17, the diet was made nearly fat-free and very low in calories, while the protein was left unchanged and no more than 1 gm. of carbohydrate was added. The plasma sugar thus was brought to normal and the acetone nearly abolished. The plasma was clear during this time, but kept its yellow color. The trifle of fat in the diet was contained only in egg-yolks, and a little additional pigment may have been derived from thrice-cooked vegetables; but it is also possible that the color was due to bile, though no hepatic or biliary disorder was suspected in this case. Though this diet contained some cholesterol, by the morning of June 18 there was a pronounced fall in both total fat and cholesterol in the blood. The stubbornness of the lipemia, however, is indicated by the fact that the lowest percentages reached for total fat were 0.83 in whole blood, 0.87 in plasma, and 0.54 in corpuscles. The ratios of total fatty acids to cholesterol and lecithin fell with the fall of lipemia.

The data of diet and urine from June 18 to Sept. 3 are given in greater detail in a paper on the use of alcohol in diabetes[5]. From June 18 to Aug. 11 the diet was kept low in fat, but by addition of alcohol the total calories were raised above the known caloric tolerance of the patient. Marked hyperglycemia, glycosuria, and slight acidosis were thus produced. The question of lipemia with a fat-poor diet under such conditions was of interest. The plasma remained clear, but a very considerable rise of its total fat occurred, up to a maximum of 3.5 % in the fasting state on July 29. This increase

Date 1917	Hour	Diet				Plasma						Total Fat			Cholesterol			Lecithin			Total Fatty Acids			Glycerides		TFA/C		TFA/L		L/C	
		Protein gm	Fat gm	CH gm.	Cal	Sugar Mg per 100cc	CO_2 vol %	Qual Acetone	Acetone + diacetic acid, mg per 100cc	B-oxybutyric acid, mg per 100cc	Total Acetone mg per 100cc	Qual lipemia	Wh Blood %	Plasma %	Corp %	Wh Blood %	Plasma %	Corp %	Wh Blood %	Plasma %	Corp %	Wh Blood %	Plasma %	Corp %	Plasma %	Corp %	Plasma	Corp	Plasma	Corp	Plasma	Corp
May 27	10.00 a.m.	—	30	—	279	233	42 3	heavy	—	—	—	Neg (oily)	1 70	2 28	0 85	0.40	0 32	0 53	—	0 10	—	1 25	2.03	0.32	1.85	—	0.34	0 60	10.58	—	0 59	—
" 28	9:00 a.m. 6:00 p.m.	60	283	—	2597	286 154	57 0 48 3	" "	— —	— —	52 1 77 3	Neg heavy	1 77 3 60	1 50 3 70	1 02 3 47	0 33 0 35	0 31 0 41	0 37 0 27	0 16 0 43	0 13 0 21	0 20 0 71	1 44 3 25	1 19 3 29	1 55 3 60	1 03 3 12	1 48 3 10	3 64 8 02	4 16 13 32	0 16 15 67	7 75 3 07	0 42 0 61	0 54 2 63
" 30	5 10 p.m.	60	253	—	2597	222	43 7	"	—	—	99 0	Faint (oily)	2 60	3 10	1 86	0 35	0 37	0 32	0 25	0 18	0 35	2 25	2 73	1 54	2 87	1 35	3.78	4 81	15 17	4 40	0 49	1 09
" 31	9 00 a.m.	60	9 5	—	332	206	48 3	"	—	—	52 1	"	1 50	2 00	0 73	0 39	0 38	0 41	0 20	0 18	0 36	1 11	1 62	0 32	1 47	—	4 26	0 78	16 20	0 88	0 26	0 88
June 3	10:00 a.m.	Fast	Day		—	228	67 0	Mod	—	—	40 8	Neg	—	2 90	—	0 37	0 42	0 29	0 23	0 15	0 38	—	—	—	—	—	—	—	—	—	0 36	1 31
" 4	10 00 a.m.	Fast	Day		—	170	58 9	"	—	—	42 3	"	1 99	1 70	2 23	0 33	0 40	0 21	0 16	0 13	0 18	1 57	1 30	2 02	1 10	1 89	3 25	0 62	10 00	11 22	0 33	0 86
" 10	10 00 a.m.	Fast	Day		—	208	64 5	Faint	—	—	43 1	"	1 30	2 00	1 09	0 34	0 29	0 44	0 17	0 11	0 21	0 93	1 71	0 85	1 58	0 53	6 90	1 48	15 65	3 09	0 36	0 47
" 11	9:00 a.m.	50	0 9	—	249	159	59 8	"	—	—	20 4	"	1 34	2 36	0 22	0 36	0 34	0 38	0 25	0 16	0 36	—	—	—	—	—	—	—	—	—	0 47	0 65
" 16	5:00 p.m.	59	1 0	1 0	255	128	—	"	—	—	13 4	Neg (yellow)	—	2 73	—	0 34	0 26	0 41	0 19	0 11	0 30	—	—	—	—	—	—	—	—	—	42	0 70
" 17	11.00 a.m.	Fast	Day		—	200	67 3	"	—	—	—	"	0 99	0 98	1 01	0 20	0 27	0 31	0 16	0 12	0 20	0 70	0.71	0 70	0 53	0 05	2 63	2 26	3 91	3 50	0 44	0 65
" 18	9:00 a.m.	59	1 0	1 0	Alcohol 280 Food 255 Total 535	113	—	"	—	—	26 6	"	0 83	0 87	0 54	0 27	0 24	0 32	—	—	—	0 50	0 63	0 22	—	—	2 62	0 68	—	—	—	—
" 24	11:00 a.m.	Fast	Day		—	164	51 3	neg	—	—	12 7	"	0 02	1 23	0 52	0 27	0 23	0 33	0 12	0 05	0 21	0 65	1 00	0 19	0 91	—	4 35	0 58	20 00	0 95	0 22	0 64
" 25	9:00 a.m.	59	1 0	1 0	Alcohol 700 Food 255 Total 955	72	67 3	"	—	—	30 3	"	0 75	—	—	0 20	—	—	0 22	—	—	—	—	—	—	—	—	—	—	—	—	—
" 30	6:00 p.m.	62	6 4	2 0	Alcohol 700 Food 340 Total 1040	156	61 7	"	—	—	15 3	—	1 25	1 59	0 71	0 24	0 23	0 23	0 24	0 14	0 39	1 01	1 36	0 48	1 23	0 22	5 97	2 09	9 71	1 23	0 61	1 69
July 22	11:00 a.m.	Fast	Day		Alcohol 700	110	71 7	"	—	—	5 9	"	1 23	1 83	0 37	0 29	0 27	0 32	0 22	—	0 44	—	—	—	—	—	—	—	—	—	0 58	1 34
" 23	9:00 a.m.	84	17	5 6	Alcohol 700 Food 527 Total 1227	159	69 2	"	—	—	16 0	"	2 40	2 90	1 57	0 27	0 23	0 32	0 10	0 09	0 11	2 13	2 65	1 25	2 81	1 22	10 60	3 91	29 44	11 36	0 36	1 54
" 29	10:00 a.m.	Fast	Day		Alcohol 665	238	70 0	"	—	—	6 6	"	2 87	3 50	1 87	0 26	0 30	0 20	0 17	0 10	0 28	2 61	3 20	1 67	3 12	1 54	10 85	8 35	32 00	5 08	0 33	1 40
Aug 4	6:00 p.m.	84	17	5 6	Alcohol 1400 Food 527 Total 1927	154	59 8	—	—	—	13 7	"	1 67	2 50	0 56	0 23	0 23	0 24	0 15	0 07	0 29	1 64	2 27	0 32	2 21	0 11	9 87	1 33	32 43	1 10	0 30	1 21
" 6	10:00 a.m.	Fast	Day		Alcohol 1190	238	60 3	—	—	—	23 7	"	1 73	1 98	1 23	0 30	0 33	0 20	0 11	—	—	1 43	1 63	1 03	—	—	4 66	5 15	—	—	—	—
" 6	10:00 a.m.	84	17	5 6	Alcohol 1400 Food 527 Total 1927	130	69 2	—	—	—	29 5	"	1 90	1 90	1 89	0 27	0 30	0 20	0 18	0 06	0.25	1 62	1 70	1 69	1 62	1 67	5 67	8 45	28 33	6 66	0 20	1 25
" 11	4:00 p.m.	84	17	5 6	Alcohol 1400 Food 527 Total 1927	217	59 8	Faint	7 3	25 1	34 4	"	1 62	1 99	0 88	0 32	0 22	0 53	0 28	0 17	0 44	1 20	1 77	0 35	1 64	—	8 04	0 65	10 41	0 80	0 77	1 83
" 12	9:00 a.m.	Fast	Day		—	278	58 9	"	13 0	24,1	37 7	"	1 99	1 96	1 98	0 25	0 25	0 24	0 18	0 14	0 27	1 74	1 71	1 74	1 58	1 63	6 84	7 25	12 21	6 44	0 55	1 12
" 13	10:00 a.m.	84	17	5 0	527	226	67 3	"	10 9	33 3	44 2	"	1 52	1 98	0 82	0 24	0 25	0 22	0 14	0 09	0 22	1 28	1 73	0 60	1 61	0 47	6 92	2 73	19 42	2 73	0 36	1 00
" 20	9:00 a.m.	50	1 8	—	212	196	67 3	neg	—	—	—	"	2 99	1 83	2 40	0 26	0 27	0 24	0 14	0 07	0 24	1 83	1 26	2 22	1 16	2 15	4 07	9 23	18 00	9 25	0 26	1 00
" 26	10:00 a.m.	Fast	Day		—	213	69 2	"	—	—	—	"	1 91	2 03	1 80	0 25	0 22	0 32	0 14	0 08	0 29	1 69	1 81	1 48	1 71	1 37	8 21	4 63	22 62	5 69	0 36	0 61
" 27	9:00 a.m.	50	1 8	—	212	187	78 7	"	—	—	—	"	2 09	2 93	0 88	0 28	0 21	0 38	0 11	0 18	0 12	1 81	2 72	0 39	2 70	0 14	12 9	1 32	27 20	4 17	0 43	0 32
Sept 2	11:00 a.m.	Fast	Day		—	118	—	Faint	—	—	—	"	2 75	3 69	1 22	0 19	0 21	0 16	0 12	0 12	0 16	2 56	3 48	1 06	—	—	16 37	8 62	29 00	8 62	0 57	1 00
" 9	10:00 a.m.	Fast	Day		—	110	73 9	neg	neg	—	10 6	10 6	1 85	2 48	1 05	0 26	0 22	0 31	0 16	0 12	0 20	1 59	2 26	0 74	2 12	0 08	19 27	2 39	18 83	3 70	0 45	0 65
" 10	9:00 a.m.	50	36	—	655	103	68 7	"	"	23 2	23 2	"	1 95	1 92	2 02	0 25	—	—	0 16	0 12	0 23	—	—	—	—	—	—	—	—	—	—	—
" 16	10:00 a.m.	1 3	0 3	6 0	33	128	63 6	"	—	—	—	"	2 78	2 95	2 48	0 37	0 33	0 42	0 22	0 15	0 33	2 41	2 62	2 06	2 30	1 02	7 94	4 93	17 46	6 21	0 45	0 79
" 17	10 00 a.m.	50	63	6 0	812	109	82 5	"	—	—	—	"	2 70	3 00	2 16	0 37	0 40	0 33	0 13	0 07	0 26	2 33	2 80	1 93	2 51	1 84	6 59	3 85	37 14	7 42	0 17	0 79

June 10.—Since June 4 diet has approximated. Protein 60gm. CH 0: fat 1-4 gm. and 275 calories.
July 23.—The fat from June 3 to August 13 was all given in the form of egg yolks.
August 4.—Beginning July 30, the diet approximated, alcohol 1400 calories, food 527 calories and total 1927 calories.
[illegible] diet started

did not continue in parallel with the other diabetic symptoms. By the morning of Aug. 12 the plasma sugar and acetone were higher than at any previous time in the alcohol experiment, but the total fat had fallen to 1.96 %. Cholesterol in general held a lower level than in the lipemia produced by fat feeding; for example, even with the maximum of 3.5 % of total fat the plasma cholesterol was only 0.3 %. The lecithin in the plasma was strikingly low, perhaps in consequence of the lecithin-poor diet, but occasional analyses in the corpuscles are noticeably high, perhaps because of the lipemia but yet not in parallel with the total fat figures. It resulted from the foregoing conditions that the ratios of total fatty acids to cholesterol and lecithin were exceptionally high.

Beginning Aug. 12, omission of alcohol gradually abolished glycosuria and ketonuria and reduced the plasma sugar to normal. The lipemia was much more resistant, and on nearly fat-free diets up to Aug. 28, and with very low fat and caloric intake up to Sept. 17, the total blood fat showed no fall and sometimes an actual rise. The analyses for cholesterol and lecithin were not greatly altered, and the ratios between these and total fatty acids remained as high as in heavy lipemia. An explanation may be complex. The overtaxing of the caloric tolerance by alcohol brought on active diabetic symptoms, including lipemia, but at the same time the sparing action of the alcohol tended to reduce the use and transport of fat. The aggravation of the diabetic state persisted long after the omission of alcohol, while at the same time the body was forced to live chiefly on its stores of fat and protein. The hyperglycemia, as an evidence of the aggravation of the diabetes, outlasted the administration of alcohol by about 2 weeks, while the hyperlipemia was more stubborn and outlasted the entire observation period of more than a month. This long duration of signs of injury is in keeping with the long duration of the excessive caloric rations. Still longer continuance of the analyses would presumably have shown a fall of the lipemia with continued low caloric diets.

Patient No. 75 was a young man with very severe diabetes, whose record has been published in detail in the previous clinical monograph[6] and in the paper on alcohol in diabetes[5]. Shortly after his admission to hospital, Feb. 21, 1917, his initial symptoms had been cleared up by the usual treatment. Exper-

Date 1917	Hour	Pro-tein gm	Fat gm	C H gm	Cal	Sugar Mg per 100cc	Uric Acid %	Qual. Ammonia	Average Diameter Acetal. mg per 100cc	Fatty Index Acetal. mg per 100cc	Total Ammonia mg per 100cc	Qual	8 a.m. Blood %	Plasma %	Corp. %	10 a.m. Blood %	Plasma %	Corp. %	12 m. Blood %	Plasma %	Corp. %	2 p.m. Blood %	Plasma %	Corp. %	Plasma %	Corp. %	Plasma %	Corp. %	Plasma %	Corp. %
May 20	10.00 a.m.			Fast	Day		170	71 1	Marl			21 0	Neg		2 25		0 19	0 49	0 55	0 47	0 23	0 07	—	1 85				4 16		8 62		0 56	0 51
* 20	4 00 p.m.	70	281	—	—	2895	221	Heavy				81 0	Heavy		4 00		0 74	0 63	0 35	0 20	0 20	0 23	—								0 67	0 58
* 27	10 00 a.m.	—	107	—	—	930	218	Slight				85 5	Slight		1 90		0 40	0 37	0 46	0 30	0 23	0 41									0 62	0 91
* 29	2 00 a.m.	70	281	—	—	2895	203	Slight				71 3	Neg	1 15	1 85	0 67	0 18	0 46	0 24	0 30	0 23	0 41	0 09	1 42	0 28	1 08	0 09	3 00	1 60	9 17	0 93	0 46	1 71
* 30	5 00 p.m.	70	281	—	—	2895	218	57 9	—	—	—	106 0	Very Heavy	—	7 28	—	0 32	0 67	—	0 28	0 33	—	—	6 71	—	—	—	11 89	—	—	—	0 63	—
* 31	9 00 a.m.	70	11	—	—	391	246	59 7	—	—	—	87 2	Faint	1 49	1 07	0 66	0 34	0 49	0 31	0 24	0 17	0 40	1 11	1 57	0 43	1 35	0 09	3 97	1 60	9 21	0 93	0 41	1 23
June 3	10.00 a.m.			Fast	Day	—	103	59 2	Faint			32 0	Neg	2 60	2 00	2 29	0 62	0 38	0 49	0 31	0 12	0 62	2 18	2 52	1 00	2 40	1 54	6 70	3 91	21 00	3 07	0 32	1 26
* 4	10.00 a.m.	70	11	—	—	391	201	63 6	*			35 6	*		2 44		0 58	0 39	0 37	0 17	0 16	0 18	—	2 05		—		5 25	—	—	—	0 41	0 49
* 10	10.30 a.m.	—	—	Fast	Day	—	170	56 0	0			12 2	*	1 14	1 09	0 38	0 29	0 27	0 20	0 20	0 15	0 29		—	—	—	—	—	—	—	—	0 56	1 08
* 11	9.00 a.m.	70	11	—	—	391	161	51 7	0			18 5	*	—	2 00	—	0 30	0 30	0 30	0 18	0 19	0 17	—	—	—	—	—	—	—	—	—	0 63	0 81
* 16	3.00 p.m.	70	11	—	—	391	164	—	0	—	—	8 3	*	—	1 72	—	0 34	0 28	0 27	0 10	0 12	0 22	—	—	—	—	—	—	—	—	—	0 41	0 81
* 17	11 00 a.m.			Fast	Day	—	182	97 3	0			—	*	0 91	0 93	0 89	0 29	0 25	0 32	0 21	0 12	0 35	0 83	0 66	0 57	0 53	0 34	2 72	1 76	5 67	1 63	0 48	1 09
* 18	9.00 a.m.	70	11	—	—	Alcohol 491 Food 391 Total 881	141	91 7	0	—	—	13 0	*	0 97	0 98	0 94	0 27	0 21	0 39	0 16	0 16	0 32	0 70	0 72	0 55	0 66	0 35	0 27	1 41	12 81	1 72	0 29	0 82
* 24	11.00 a.m.			Fast	Day	Alcohol 700	98	57 0	0	—	—	7 2	*	0 85	0 93	0 72	0 29	0 28	0 43	0 11	0 10	0 13	0 66	0 73	0 29	0 61	0 21	2 60	0 97	7 30	2 23	0 50	0 29
* 28	9.00 a.m.	70	11	—	—	Alcohol 700 Food 391 Total 1091	96	72 1	0	—	—	19 1	*	0 91	0 91	0 93	0 24	0 20	0 31	0 18	0 10	0 31	0 66	0 71	0 02	0 89	0 42	2 55	2 00	7 10	2 00	0 80	1 00
July 1	10.00 a.m.	1 1	0 4	3 6	—	Alcohol 700 Food 21 Total 721	111	—	0	—	—	—	*	0 83	0 86	0 75	0 16	0 17	0 13	0 11	0 11	0 19	0 64	0 69	0 62	0 57	0 58	4 06	4 80	9 27	0 20	0 95	0 77
* 3	10.00 a.m.	77	17	—	—	Alcohol 700 Food 470 Total 1170	126	64 5	0	—	—	—	*	0 83	0 86	0 75	0 23	0 16	0 11	0 18	0 07	0 36	0 60	0 70	0 44	0 61	0 20	3 88	1 42	10 00	1 22	0 37	1 10
* 28	3.00 p.m.	98	24	—	—	Alcohol 1828 Food 615 Total 2443	123	58 9	0	—	—	29 6	Faint	1 82	2 87	0 20	0 25	0 27	0 23	0 22	0 29	0 27	1 57	2 00	0 06	—	—	9 62	3 84	13 60	0 22	0 74	1 17
* 26	10.30 a.m.			Fast	Day	Alcohol 1400	122	60 3	—	—	—	38 4	Neg	0 96	1 41	0 34	0 24	0 21	0 28	0 24	0 10	0 26	—	—	—	—	—	—	—	—	—	0 46	0 93
* 30	9.00 a.m.	93	151	—	—	Alcohol 1400 Food 1789 Total 3189	164	60 9	—	—	—	27 1	*	0 93	0 97	0 91	0 24	0 21	0 38	0 26	0 13	0 41	0 71	0 76	0 53	0 60	0 28	3 01	1 60	8 05	1 29	0 71	1 08
Aug 4	5.10 p.m.	98	151	—	—	Alcohol 1400 Food 1789 Total 3189	189	—	—	Faint	—	49 0	Faint	1 19	1 76	0 57	0 27	0 22	0 29	0 29	0 25	0 34	0 97	1 53	0 37	1 32	0 24	6 65	1 65	8 12	1 00	1 00	1 70
Aug 5	10.00 a.m.			Fast	Day	Alcohol 1400	149	72 1	—	—	—	35 6	Neg	0 93	1 40	0 11	0 21	0 22	0 19	0 10	0 10	0 25	0 72	1 15	—	—	—	8 30	—	7 28	—	0 73	1 32
* 11	4.00 p.m.	93	151	—	—	Alcohol 1400 Food 1789 Total 3189	112	68 4	—	10 6	27 0	37 9	Faint	1 72	1 82	1 37	0 27	0 22	0 26	0 21	0 21	0 21	1 45	1 67	1 01	1 50	0 90	7 60	2 80	7 95	4 00	0 95	0 58
* 12	9.50 a.m.			Fast	Day	—	212	—	Faint	9 8	17 3	20 8	Neg	—	1 76	—	0 29	0 20	0 45	0 10	0 16	—	—	—	—	—	—	—	—	—	—	0 80	—
* 13	10.00 a.m.	93	151	—	—	1789	192	72 1	0	9 3	23 0	31 3	*	—	2 46	—	0 25	0 25	0 25	0 24	0 17	0 37	—	—	—	—	—	—	—	—	0 94	1 45
* 19	9.00 a.m.	93	19	—	—	Alcohol 1240 Food 945 Total 1791	151	67 3	—	21 4	22 8	44 2	*	—	1 90	—	0 25	0 28	0 19	0 12	0 10	0 00	—	—	—	—	—	—	—	—	—	0 57	0 21
* 21	9.00 a.m.	93	2	—	—	Alcohol 1240 Food 455 Total 1701	270	54 8	0	6 8	22 4	27 2	*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
* 24	6 45 a.m.	93	7	—	—	Alcohol 1246 Food 455 Total 1701	370	65 8	0	Trace	18 4	18 4	*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	9 45 a.m.						345	64 5	0	*	19 6	19 6	*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	12 45 a.m.						212	60 7	0	*	10 7	10 7	*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	5 00 p.m.						250	54 1	0	*	19 0	19 0	*	3 07	3 76	1 92	0 26	0 25	0 27	0 22	0 21	0 24	2 81	3 53	1 35	2 44	1 24	14 12	5 00	16 90	5 62	0 84	0 89
* 25	9 30 a.m.	93	7	—	—	Alcohol 1240 Food 455 Total 1701	400	59 8	0	*	11 4	11 4	*	1 53	1 60	0 41	0 27	0 29	0 20	0 19	0 12	0 24	1 20	1 67	0 21	1 52	0 04	5 75	1 80	12 84	0 88	0 41	1 20
	10 15 a.m.						384	48 6	0	*	10 4	10 4	*	2 05	1 77	2 39	0 26	0 23	0 32	0 27	0 17	0 47	1 79	1 54	2 27	1 40	2 04	6 70	7 09	9 04	4 83	0 74	1 47
	11 45 a.m.						344	60 7	0	*	20 4	20 4	*	1 70	1 46	1 80	0 25	0 23	0 29	0 31	0 17	0 56	1 45	1 61	1 21	1 47	0 84	7 00	4 17	9 48	2 06	0 74	2 02
	5 00 p.m.						278	53 8	0	0	11 5	11 5	*	2 60	2 50	1 78	0 24	0 21	0 32	0 25	0 16	0 32	2 36	2 09	1 45	2 63	1 14	12 61	4 20	16 81	2 70	0 76	1 57
* 27	10.00 a.m.			Fast	Day	Alcohol 1246	344	59 6	0	0	2 5	2 5	*	1 80	1 84	1 21	0 22	0 23	0 23	0 23	0 16	0 38	1 37	1 61	0 98	1 45	0 75	7 00	4 26	10 62	2 38	0 84	1 65
Sept 2	11.00 a.m.			Fast	Day	Alcohol 700	278	—	Faint	—	—	—	*	0 80	1 38	—	0 23	0 17	0 41	0 14	0 07	0 31	—	—	—	—	—	—	—	—	—	0 61	—
* 3	11.00 a.m.	60	27	—	—	Alcohol 356 Food 470 Total 826	159	71 0	0	—	—	—	*	1 56	1 87	0 91	0 23	0 17	0 44	0 10	0 09	0 34	1 33	1 70	0 57	1 64	0 35	10 00	1 87	21 25	1 68	0 47	1 00

REMARKS

May 21—Cholesterol-free diet begun
July 28—Fat, 14gm. in the form of eggs and also fat 14gm. in the form of veal.
July 30—Fat 21.8 gm. in the form of eggs
Fat 104.0 gm. in the form of butter
Aug. 16—Cholesterol and lecithin-free diet begun

imentally, glycosuria and ketonuria were then restored by feeding beyond the caloric tolerance first with fat and later with alcohol. The analyses of May 20 were performed after 16 days of a preliminary diet of 70 gm. protein and 1500 calories, without carbohydrate. It will be noticed that the plasma of a fasting blood sample contained 0.179% sugar and 2.25% total fat, while the percentages of cholesterol and lecithin were within normal limits.

May 21 to 30, the fat ration was raised to a maximum of 281 gm., and instead of a fast-day 100 gm. of olive oil was given on May 27. In a blood sample taken during digestion on May 26, the plasma was creamy and contained 4.0% total fat; lecithin was slightly increased but cholesterol was practically unchanged. In a fasting sample the next day the lipemia was lower. May 28, the plasma was clear before breakfast and contained 1.84% total fat, while at 6:30 P. M. it was very creamy and contained 8.0% total fat. On the afternoon of May 30 the percentage was 7.28. Both cholesterol and lecithin remained little changed. The ratios of total fatty acids to cholesterol and lecithin rose enormously, as usual in heavy lipemia. This lipemia developed in conjunction with other symptoms of active diabetes.

May 31 to July 17, the diet was made very low in fat and total calories and as free as possible from cholesterol. Glycosuria and acidosis ceased and the plasma sugar fell, though not fully to normal. The concentration of all the blood lipoids also fell, the most persistent elevation being that of the total fat, which remained at 0.93% in the plasma on June 17.

Beginning June 18, the fat-poor, cholesterol-free diet was continued but the calories were increased by addition of alcohol. It is noticeable in Table V that the plasma sugar fell to 0.098% on June 24 and to 0.066% on June 25. The reason was probably two-fold: first the diet, which was still rather low in calories and within the patient's tolerance, and second the effect frequently shown by alcohol in depressing the blood sugar at least temporarily. It is worth noting that this reduction of blood sugar was not accompanied by any special raising or lowering of any of the blood lipoids. This same general character of the diet, together with low figures for blood sugar and fat, continued through July 2.

Following July 2, the protein ration was increased, also the fat intake was raised to 22 or 25 gm. daily and the restrictions against cholesterol were omitted. By July 28, acetone was appearing in blood and urine, but the plasma sugar was still normal, perhaps partly because of the special depressing influence of alcohol already mentioned. Lipemia was present during digestion at 5 P. M., to the extent of 2.87 % of total fat in the plasma. In the fasting plasma of the next morning the percentage of fat, namely 1.41, was still above normal. The figures for cholesterol and lecithin were still not greatly changed.

July 30 to Aug. 15, the diet of protein and alcohol was enlarged by the addition of 151 gm. of fat, given chiefly in the form of butter and eggs so as to be rich in cholesterol and lecithin. This excessive caloric intake gave rise to hyperglycemia, glycosuria and ketonuria. The plasma remained clear, though its content of total fat rose as high as 2.48% on Aug. 13. Again the percentages of cholesterol and lecithin were not greatly changed, except for occasional high values in the corpuscles. Here it is uncertain whether the alcohol had any influence in depressing the lipemia which might otherwise have developed.

From Aug. 16 to the end of the record, the diet was kept very low in fat and free from cholesterol and lecithin. Hyperglycemia and glycosuria persisted because of the comparatively high caloric intake up to Aug. 27. After this date the diet was reduced so as to contain from 587 to 820 calories daily, and the plasma sugar by Sept. 3 had accordingly fallen to 0.159 %, with glycosuria absent. The simple omission of fat, cholesterol and lecithin did not suffice to reduce the lipemia, which on Aug. 24 to 27 (i. e., after more than a week of the fat-poor diet) was as high as during the preceding period of high fat. The percentages of cholesterol and lecithin were also as high as before. The subsequent reduction of total calories likewise failed to reduce greatly the figures for total fat or lecithin, though those for cholesterol fell slightly. This behavior conforms to the rule that the lipemia of severe diabetes is more stubborn than any of the other chemical symptoms in coming under complete control. Evidently a much longer period of low diets would have been required to reduce the blood fat to any level near normal.

Conclusions

As these experiments represent only a small fragment saved from the much larger research which was attempted, the following tentative conclusions are mostly negative in character.

1. The name *lipemia* is justified by the fact that neutral fat is the principal substance which accumulates in the blood. The higher the lipemia, the higher is the ratio of the glycerides to other lipoids such as lecithin and cholesterol.

2. The quantitative excess of fatty substances is obviously the chief cause of the milky turbidity of the plasma. Comparisons between the colums for "qualitative lipemia" and the analytical figures in these tables, however, confirm the statements of former writers that samples of plasma containing a marked excess of fat may be clear, while others containing much less fat may be turbid. No definite relations have been found between the various lipoids to explain these differences, though it is still possible that a more complete study might have thrown light on the question. These analyses show only that the ratios between the different lipoids are subject to wide variations.

3. The fragmentary results, and the loss of the analyses in normal controls, prevent any conclusion concerning the Leathes-Bloor hypothesis that lipemia is due to a failure of the mechanism whereby the red corpuscles take up the fat after its absorption and convert it into lecithin or other forms suitable for assimilation.

4. The combination of active severe diabetes and a high fat diet is undoubtedly most conducive to lipemia. Some degree of lipemia, however, may be reckoned among the most stubborn symptoms of severe diabetes, and may persist for at least several weeks after disappearance of both hyperglycemia and acidosis, on diets very low in fat and total calories.

5. Diets high or low respectively in cholesterol or lecithin have shown no decisive influence in either producing or clearing up lipemia. Diabetic patients or animals, known to be subject to lipemia, have not shown any remarkable retention of cholesterol in the blood when fed cholesterol or cholesterol-rich foods.

6. No uniform parallelism has been found between the

sugar or acetone in blood or urine and the accompanying degree of lipemia. The same is true of the CO_2 capacity of the plasma. Also, the giving of carbohydrate or its exclusion from the diet seems not to be a determinig factor in lipemia.

7. The observations with alcohol are suggestive but incomplete. When active diabetic symptoms are restored by an excessive caloric diet composed essentially of protein, carbohydrate and alcohol, a definite though moderate lipemia seems to result as one of the active symptoms. It is undecided whether alcohol has any specific influence in lowering lipemia, comparable to its occasional temporary action in reducing hyperglycemia and glycosuria.

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EXPERIMENTAL STUDIES IN DIABETES

Series IV. Lipemia. 2. The production of diabetic lipemia in animals, and observations on some possible etiologic factors

By FREDERICK M. ALLEN, M. D.

The study of fat metabolism has been greatly advanced in recent years by the introduction of convenient micro-analyses for the various lipoids. Chiefly Bloor, and to a less extent Bang and others[92, 118, 258, 268, 313, 373], have developed this technic and applied it in important researches. Furthermore, in contrast to carbohydrate and protein, which only in isolated instances (e. g. glycogen, and the protein "Mast" of liver cells) can be studied by any but chemical means, fat is a substance which can be followed in various stages of its transport and storage by direct microscopic observation, and the methods for its morphologic demonstration and the differentiation of the several lipoids by staining reactions have been industriously developed and applied[1, 109, 330, 342, 350, 356]. Parts of the literature pertaining to fat metabolism and diabetes were reviewed by the writer[8] in 1917. Reviews have been published by Magnus-Levy and Meyer[232] and by Bloor[67] of fat metabolism and transportation, by Forbes and Keith[121], by Landsberg[205] and by Levene and Rolf[213] of the phosphatids, and by others[250, 269, 340] of cholesterol metabolism. These large bibliographies, which should be consulted to supplement that of the present paper, show the vast amount of work that has been done in this field. Nevertheless, the multitude of investigations by both chemical and anatomical methods have failed to afford any such clear conception of fat metabolism as exists for carbohydrate and protein metabolism. It is noticeable that Bloor in the review mentioned has recorded only a few facts as firmly established. There is possible instructiveness in a survey of the subject by an opposite method, viz: an

enumeration of some of the unknown or disputed points in the successive stages of the physiological and pathological fat economy, as follows:

I. Normal fat metabolism.

(1).—The intestinal function for fat.
(2).—The passage of fat from the epithelium to the lacteals.
(3).—The cycle of fat in the blood.
(4).—The taking up of fat by the tissue cells.
(5).—Storage and disposal of fat in the tissues.
(6).—Specific properties of fats and lipoids.
(7).—The metabolism of lecithin.
  a. Sources of lecithin.
  b. Relation of phosphatids to neutral fats and cholesterol.
  c. Disposal of lecithin by the tissues.
  d. Functions of the phosphatids.
(8).—The metabolism of cholesterol.
  a. Sources of cholesterol.
  b. Relation of cholesterol to neutral fats and phosphatids.
  c. Forms of cholesterol in the blood.
  d. Excretion of cholesterol.
  e. Storage of cholesterol in the tissues.
  f. Organs of cholesterol metabolism.

II. Pathological fat metabolism.

(1).—The origin of lipemia.
(2).—Lactescence of plasma.
(3).—Fattiness of organs.
(4).—Pathological conditions caused by fatty acids.
(5).—Pathological lecithin metabolism.
(6).—Pathological cholesterol metabolism.
  A. Cholelithiasis.
  b. Renal and vascular disorders.
  c. Diabetes.
  d. Experimental lipemia.
  e. Local accumulations of cholesterol.

(1).—*The intestinal function for fat.*—It is not necessary to go so far as to mention the poorly understood action of the bile[93, 146], or Lombroso's disputed hypothesis that an internal pancreatic secretion is necessary for fat absorption[166, 217, 218, 261, 284, 305]. Granting that fats are completely split in digestion preliminary to absorption, it remains unproved whether they are absorbed as free acids or in soaps or other compounds, and the mechanism whereby they are taken up by the epithelium is also unknown. The alimentary epithelium of fasting animals has been shown to contain fat globules at certain times, sup-

posedly as a phase of the metabolism of the cells[263] . This may possibly be connected with the excretion of fat into the intestine[154, 161]. In certain conditions, for example experimental diabetes (Lombroso), these phenomena may perhaps be exaggerated. During digestion, all observers are agreed that no visible fat is ever found in the striated margin of the cells bordering the intestinal lumen. The fat evidently passes through this marginal zone in some invisible and unstainable form, and becomes visible first in the form of fine droplets in the protoplasm adjoining this zone. As the fat passes toward the base of the epithelial cell it collects into larger globules. Presumably within these cells it undergoes some degree of chemical change. Free fatty acids given in the diet are combined into neutral fats by means of glycerol derived from the diet (only within narrow limits from the body cells)[26, 255] and foreign fats are partially changed in the direction of a closer resemblance to the natural body fat of the species[75, 153, 201, 229, 343].

(2).—*The passage of fat from the epithelium to the lacteals.*—The details of this process also remain undemonstrated. Passage of droplets out of the epithelium has not been observed. The theory of transportation by leukocytes appears improbable. Any chemical theory requires the assumption that the fat assumes some invisible form in its passage out of the epithelial cells and becomes again visible in the tissue spaces and lymphatic capillaries.

(3).—*The cycle of fat in the blood.*—Chemical analyses show that the blood fat ordinarily is nearly constant, as though regulated by some delicate mechanism, but it is increased during fat digestion in most species[55, 67, 114, 128, 208, 237, 325] (not in rabbits[25, 271] or fowls[368]). It has long been known that the absorbed fat is carried as an emulsion of fine globules through the thoracic duct[337], but its changes after entry into the blood stream remain a mystery. Only surplus quantities in excess of the combining power of the blood remain visible in droplet form as the so-called hemoconia[212, 271]. By far the greater part of the fat assumes an invisible form, not soluble in ether or stainable with fat stains, and demonstrable only after precipitation or digestion of the blood proteins[271, 272, 273]. The nature or composition of this compound is unknown. It has appeared to both earlier and later investigators that the red corpuscles are concerned in this transformation[56, 57, 67, 83]. There is an increase of fat in the red corpuscles as well as in the plasma, and in certain stages the concentration is found actually higher in the former than in the latter. The hypothesis that the corpuscles change the fat and return it to the plasma in the form of lecithin remains unproved. Otherwise, not even hypotheses exist for these phenomena.

(4).—*The taking up of fat by the tissue cells.*—The mode of passage of fat through the cell wall again remains unknown. There is still some belief in a uniform doctrine of lipase action, viz: splitting of fats for absorption from the bowel, another splitting for their passage from the epithelium to the lacteals, and a third splitting for their passage from the blood into the tissue cells. In addition to the apparent

cumbersomeness of such a process of repeated hydrolysis and synthesis, objections to this theory are found in the scanty quantity and slow action of demostrable lipases in either the blood or most tissues[37, 38, 43, 48, 70, 71, 73, 123, 139, 286, 291, 302, 304, 320, 321]. Most plausible at present appears the Leathes-Bloor hypothesis that lecithin is the metabolic form of fat, and that fat passes through the cell membrane and enters the protoplasm for utilization in this form[56, 57, 64, 67, 287]. If full confirmation is obtained of the remarkable finding by Meigs, Blatherwick and Carey[242] that the mammary glands derive their fat supply from the lecithin of the blood, and that they secrete most of it as neutral fat in the milk and return most of the phosphate in inorganic form to the blood, a strong presumption must exist that other tissues derive their fat supply in similar manner[294, 369].

(5).—*Storage and disposal of fat in the tissues.*—When fat is utilized for energy production, the nature and stages of its oxidation are covered only by hypotheses, supported by the most fragmentary proof[189]; but it thus passes outside the domain of lipemia. Demonstration of direct oxidation of fat not only by the liver[219] but also by the nervous system[156] has been reported. Storage of fat in the tissues is a complex and obscure process. It is known that parenchymal cells in the liver, kidney, and various other organs contain fat in the form of larger or smaller droplets, and that this infiltration may be increased by increase of fat metabolism, as with fat-rich diets, or fasting[247, 248, 342]. All protoplasm also contains fat in invisible and unstainable forms, not extractable by ordinary solvents, as noted in the blood[73, 101, 150, 235]. The influences governing the changes from the invisible to the visible form and *vice versa* are little understood. The storage of fat in adipose tissue is not a random stuffing with inert pabulum. Slight physical and chemical differences distinguish the depot fat of different parts of the body, omental or perirenal fat, for example, being slightly different from subcutaneous fat[34, 87]; also changes occur in the stored fat. If the depots are filled by heavy feeding of a foreign fat and normal diet subsequently resumed, the foreign fat is replaced in the course of weeks or months by the forms characteristic of the species. The regulation of fat mobilization and the nature of the stimulus causing parenchymal cells or adipose tissue cells to build up or break down their fatty stores are also unknown.

(6).—*Specific properties of fats and lipoids.*—The question of the indispensability of lipoid substances in the diet is still disputed. The desirability of a fairly liberal proportion of fat in the diet of children and adults is recognized[17, 32, 49, 143, 145, 346], but it has been shown that a minimal fat intake may be compatible with health[155, 274, 275, 276, 277, 278]. The fatty foods are known to be important carriers of vitamines, and it appears probable that vitamines are stored along with the fat of certain organs, as in the case of codliver oil. Osborne and Mendel have shown that growth can occur on diets extremely low in fats. Stepp on the other hand described deficiency disorders due to the absence of lipoids, independent of any of the known vitamines. He considers that the vitamines are only a few of many complex organic substances

necessary to maintain life[299. 347. 348. 349. 350. 352]. The suggestion has been made on the basis of embryology and anatomic structure that special portions of the adipose tissue constitute glands of internal secretion[87. 88. 89].

(7).—*The metabolism of lecithin.*—Reference may again be made to the reviews by Forbes and Keith[124], Landsberg[205] and Levene and Rolf[213]. The lack of knowledge of almost the entire physiology of the phosphatids is indicated by an enumeration of unknown points, as follows:

a — *Sources of lecithin.* — It is well known that the phosphatids can be freely synthetized in the animal organism. The disposal of food lecithin is less certain. It can evidently be decomposed in digestion, but whether it is absorbed as split products, or at least in part as unchanged lecithin, is not fully certain. If absorbed as cleavage products, these are evidently re-synthesized, as most evidence favors the view that lecithin feeding causes an increase of lecithin both in blood and in certain organs[6. 125. 303. 340. 375]. An actual secretion of lecithin by certain organs is unproved[236].

b — *Relation of phosphatids to neutral fat and cholesterol.* — Physiological increases of fat or cholesterol in the blood seem generally to be accompanied by a corresponding increase of lecithin, even on lecithin-poor diet[25. 56. 67. 116. 157. 287. 288]. In pathological conditions, lipemia seems to be always accompanied by lecithinemia, but a rise of cholesterol does not necessarily entail a rise of lecithin in the blood. The link is therefore evidently between fat and lecithin rather than between cholesterol and lecithin, but the meaning of the association is not established. The increase of lecithin is sometimes specially marked in the red corpuscles, and the hypothetical relation to fat metabolism was previous mentioned.

c — *Disposal of lecithin by the tissues.* — The question whether all fat must pass through a lecithin stage in order to be metabolized is the outstanding one. The variable quantities of phosphatids in different tissues under different conditions have received some atttention[231] but are not understood. The organs suspected of playing a special role in lecithin metabolism are essentially the same as in the case of cholesterol (liver, adrenals, corpus luteum, etc.)[6. 121. 125].

d — *Functions of the phosphatids.* — It is a hackneyed statement that the occurrence of lecithin and cholesterol in every living cell must denote some high biological importance of these lipoids. The large percentages in the nervous system presumably have some special significance[192. 213. 273]. The existence of jecorin as a true compound of lecithin and glucose has been disproved[35. 36. 238. 240. 241. 283. 329. 333]. Cephalin has been shown to be an important factor in blood coagulation[137. 213]. There are suggestive hypotheses that the lipoids are essential to the emulsion structure of protoplasm[193], and also that they activate or neutralize toxins[15. 167. 199. 211. 240. 269. 374. 375], favor the action of enzymes[15. 18. 69. 146. 171. 198. 206. 213. 244. 286. 345], stimulate organ activities[94. 362] or development[148. 298. 300], or serve as intermediaries for various molecular transformations. As proof is lacking, the whole problem remains unsolved.

(8). — *The metabolism of cholesterol.* — Owing to the comparatively simple methods available for analysis, the investigations of cholesterol metabolism have been particularly numerous and constitute a large literature in themselves. But ignorance of this subject has not been greatly lessened, as shown by the following enumeration:

a — *Sources of cholesterol.* — The fetus has a source of cholesterol in the maternal blood [162, 339], and the suckling in milk[98]; but definite proof seems now to exist that cholesterol may at least sometimes be synthesized by the organism [129, 227]. The chemical possibility of a synthesis from oleic acid was shown by Lifschütz[214]. The level of blood cholesterol is governed largely by the food of the individual or species, and there is still a basis for the older view that under ordinary conditions the animal and vegetable sterols of the diet are the principal source of cholesterol for the body [126, 130, 141, 160, 165, 210, 227, 285, 293, 317, 351]. The process of digestion and absorption has not been elucidated. Presumably, cholesterol esters are broken up in digestion. Absorption or re-formation of the esters was indicated by researches showing increase of the esters in the chyle or blood [175, 203, 251, 252, 293] after cholesterol feeding, but this view has been shaken or overthrown by Knudson[191], who found an increase of only free cholesterol in the blood when either the free form or the esters were fed, and explained the former contrary findings as due either to an admixture of fat in the diet or to continuance of the feeding experiments over a considerable number of days, thus permitting a secondary equilibrium to be reached between the free and esterized cholesterol. The origin of the cholesterol esters is then unknown, both the red corpuscles and the tissue cells being hypothetical sites of their formation. The pharmacology or toxicology of cholesterol injections is doubtful[72, 94, 95, 99, 186, 194, 267, 273].

b — *Relation of cholesterol to neutral fats and phosphatids.* — As already mentioned, every rise of cholesterol in the blood seems to be associated with an elevation of total fat and phosphatids, except under pathological or artificial conditions. The converse relation, namely that a rise of cholesterol accompanies every increase of fat in the blood, is improbable according to the weight of present evidence [25, 29, 67, 157, 287, 288, 293, 358]. Several observations that the alimentary lipemia following ingestion of cholesterol-free fat is attended with an increase of blood cholesterol have been contradicted by Bloor and Knudson[59, 67]. The ratio of cholesterol to lecithin remains fairly constant ordinarily, but is subject to marked variations under special conditions.

c — *Forms of cholesterol in the blood.* — It is recognized that cholesterol is constantly present in both free and ester form in the plasma, the ordinary proportions being about 58% of the esters and 42% of the free form. Free cholesterol is an important constituent of the red corpuscles, and has been found in still higher percentage in leukocytes [322, 367]. The occurrence of cholesterol esters in the red corpuscles is in dispute. Most leading authors heretofore have agreed that all cholesterol in the corpuscles is free [53, 160, 293, 367] though the presence of esters in sheep[172], dog and human corpuscles has been reported by some [24, 311]. Knudson [190] on the contrary has found that during

digestion of a neutral fat, though the total blood cholesterol remains unchanged, a considerable increase of cholesterol esters takes place in the blood, including both plasma and corpuscles. The presence of the esters in the corpuscles under these circumstances suggests a function of the corpuscles and of cholesterol in fat assimilation. The significance of free and esterified cholesterol and of the balance existing between them is unknown[53, 293, 319, 326, 366].

d — *Excretion of cholesterol.* — Though cholesterol is essential to life, its final disposal seems to be chiefly or wholly as a waste product. All evidence agrees that it is decomposed only with difficulty by the fluids or tissues of the body, and in contrast to lecithin it is of no importance as a source of energy. The only important channel of excretion is through the bile. The cholesterol content of the bile of different species and of individuals on different diets and under other different conditions seems to vary with that of the blood[14, 99, 104, 130, 267, 315, 316, 317, 351, 371]. In addition, the opinion has been advanced that the liver breaks down cholesterol into bile acids[215]. The cholesterol entering the bowel in the bile is partly reabsorbed and partly excreted in the feces. Its possible functions during the cycle remain unknown.

e — *Storage of cholesterol in the tissues.* — Cholesterol is stored in small quantities along with the neutral fat in adipose tissue. The significance of the large quantities of cholesterol in the nervous system and smaller percentages in all other organs is unknown. The anisotropic cholesterol esters demonstrable in various organs, such as the kidneys, were a striking morphologic discovery of the Aschoff school[18, 46, 121, 173, 174], but their function or meaning is unknown[250].

f — *Organs of cholesterol metabolism.* — The liver[81, 266, 315, 316], the adrenal cortex[79, 187, 200, 202, 203, 239, 253, 316, 354], the sex organs, [219, 220, 222, 260, 323] (especially the corpus luteum), [78, 134, 135, 185, 324] and other organs have been credited with special endocrine relations to cholesterol. It is known that these organs can be greatly enriched with cholesterol by means of forced cholesterol feeding. The liver, for example, actively takes it up from the blood[194, 203], and the adrenal cortex and corpora lutea of rabbits may enlarge enormously by reason of retained cholesterol[196, 266]. Inasmuch, however, as both free and esterized cholesterol may increase markedly in the blood after either single or double epinephrectomy, the hypothesis that the adrenal cortex serves for either the production or the esterification of cholesterol is untenable[159, 185, 203, 220, 314].

g — *Functions of cholesterol.* — The theories or speculations concerning cholesterol are of the same order as those previously mentioned for phosphatids[18, 69, 77, 94, 95, 126, 151, 159, 160, 176, 177, 178, 186, 201, 243, 245, 252, 269, 286, 297, 298, 312, 340, 353]. Some role in fat metabolism is plausibly assumed to be one of its uses[159, 160].

As the physiology of fat metabolism is so poorly understood, the obscurity necessarily becomes still greater when pathological changes enter. Various points of ignorance or dispute may again be enumerated as follows:

(1) — *The origin of lipemia.* — In two of the heaviest experimental forms, viz: the lipemia of stuffed geese [52] and the lipemia of rabbits kept on diets high in cholesterol and fat, it is known that the source of the blood fat is the food. In another heavy form, viz: the anemic lipemia of rabbits it is equally clear that the origin of the blood fat is from the tissue fat [68, 119, 158, 321]. In the most intense form of clinical lipemia, viz: that of diabetes, the derivation of the circulating fat is from the food [8, 138, 164, 182, 183, 232, 270, 288, 292]. The origin of the less marked lipemia in some cases of nephritis [47, 61, 77, 105, 106, 151, 249] is not established. Minor grades of lipemia occurring in the early days of fasting, with exercise, in poisoining with phlorizin, phosphorus, alcohol, chloroform, arsenic and other drugs, and in some diseases, presumably represent chiefly increased fat transport [27, 39, 55, 117, 138, 144, 207, 208, 256, 257, 321]. The point in common between these different disorders is unknown, and the reason why the food fat is impeded in its passage out of the blood, or the tissue fat is mobilized and thrown into the blood in excess, is a problem which is not covered even by intelligent hypotheses.

(2) — *Lactescence of plasma.* — It has been observed by several authors that the gross appearances of lipemia are unreliable [42, 43, 58, 115, 158, 249]. Turbidity always indicates high fat content, but not *vice versa* [372]. A plasma which is entirely clear may sometimes contain higher percentages of fat or lipoids than another plasma which is markedly turbid. As noticed by Bloor [58, 68] and others, the turbidity sometimes develops on standing. No cause of this phenomenon has yet been found in any special relation between the different lipoids [197], or in impoverishment of blood proteins, or other known chemical changes. An answer to the question might conceivably afford some clue to a better understanding of fat assimilation.

(3) — *Fattiness of organs.* — The original theory of fatty degeneration in the sense of transformation of protoplasm into fat has been abandoned, but is occasionally revived in some modified form. Fatty infiltration, viz., the deposit in the cells of fat from the blood, is known to be the common process, but the cause and meaning remain unknown. The phanerosis of fat, viz. its change from the invisible to the visible form in the cell, is another recognized cause of the fatty appearances. The observation that these changes are favored by lack of carbohydrate, and are more or less preventable by carbohydrate, fails to explain the nature of the process or even the rôle of the carbohydrate [133, 306, 307, 308, 309, 310]. The liver is known as the organ preeminently disposed to these changes, supposedly because of its important function in fat metabolism [114, 147, 246]. Fatty deposits are also prominent in certain cells of the kidneys [46, 99, 123, 248], especially in the Henle tubules, and in diabetes the resulting vacuoles are sometimes wrongly interpreted as representing glycogen deposits. There is no adequate information concerning the reasons for preponderance of lecithin, cholesterol or glycerides in fatty changes of organs [1, 121, 141, 168, 170, 173, 174, 179, 194, 195, 292, 330, 331, 359, 366, 373].

(4) — *Pathological conditionss caused by fatty acids.* — Fatty acids

are harmless and well utilized when mixed in the diet in moderate quantities, but irritate the intestine when taken in large quantities [45, 102]. Both fatty acids and soaps are highly toxic if allowed to enter either the blood or the tissues in unchanged form [2, 180, 255]. For this reason a protective distoxication by combination with glycerol is known to be necessary, and has been assumed also with lecithin and cholesterol [252]. The strong hemolytic action of soaps and fatty acids has brought them under suspicion in the etiology of Bothriocephalus, pernicious and other anemias [112], but the proof has failed [45, 60, 91]. No pathological conditions have ever been demonstrated as due to poisoning by any fatty substances.

(5) — *Pathological lecithin metabolism.* — Every pathological lipemia is accompanied by a rise of cholesterol in the blood, but Bloor emphasized the fact that lecithin fails to maintain its full ratio with neutral fat, so that with increasing lipemia the absolute value for lecithin increases, but the ratio of lecithin to neutral fat progressively falls; also, that the rise of fat in the plasma is not matched by a corresponding rise in the corpuscles, as in normal (alimentary) lipemia [58, 61, 65, 127, 158]. The question whether these findings indicate a breakdown of a normal lecithin mechanism of fat assimilation remains doubtful. All lipoid analyses may be low in plasma or corpuscles in cachexia or anemia, but no real light has thus been shed upon the problem of anemia [42, 60]. Other supposed abnormalities involving lecithin are still less tangible. The suggested balance or antagonism between lecithin and cholesterol in connection with infections, intoxications, hemolysis, etc. receives no practical support from the observations on lipemia, where the high or low values for either group of lipoids seem to create no special susceptibility or immunity. Numerous other speculations concerning the rôle of lecithin or proposals for its therapeutic use have failed of proof [281].

(6) — *Pathological cholesterol metabolism.* — The cholesterol concentration of the blood or organs may be subnormal with diets poor in cholesterol and fat [185, 311, 312, 358] and also in certain intoxications [27] and diseases, especially pernicious anemia [46, 50, 90, 176, 178, 233, 234, 279, 336, 353], severe acute infections [5] or chronic states of emaciation [21, 40, 44, 80, 152, 177, 128, 204, 222, 227, 337, 366]. This decrease may appear the more serious when it involves not merely the plasma but also the chemical constitution of the corpuscles, but even here the harm is suspected rather than proved, and some populations seemingly thrive with blood cholesterol concentrations ordinarily classed as subnormal [96]. The pathology of cholesterol consists chiefly in elevations above normal in blood and tissues, as reported especially in cholelithiasis, renal and vascular disorders, diabetes and the experimental lipemias [21, 29, 40, 42, 44, 57, 59, 61, 77, 80, 84, 97, 115, 136, 204, 233, 234, 280, 326, 338, 357]. There is no direct relation between the sugar and the fat or cholesterol of blood [30, 67, 262, 324]. The disturbances of blood cholesterol, as also the subject of cholesterol deposits in tissues, may receive special mention as follows:

a — *Cholelithiasis.* — Extending the work of a number of authors [76,

99. 223. 224 who had found relations of high blood cholesterol concentrations with cholelithiasis or with jaundice from any cause, Rothschild 317. 318. 319 set up the most complete hypothesis of a constitutional defect of cholesterol metabolism underlying many cases of gallstones, and explained many contradictory findings by the demonstration that cholesterol-poor diet, operative drainage of the gall-bladder, or infection may reduce the typically high blood cholesterol of such cases. It is uncertain if all the discrepancies are thus accounted for, especially as reliable observations have shown that elevation of the blood cholesterol is far from a constant finding with gall-stones, and its diagnostic value has been questioned 97. 136. 280. 289. 327. Perhaps not enough attention has been given to the possibility that stones and other disturbances in the bile passages may be the cause rather than the result of accumulation of cholesterol in the blood, through interference with the natural channel of excretion, or to the variable composition of gallstones, which may cast doubt upon a theory of their sole origin in a cholesterol dyscrasia. Analyses in Eck fistula dogs, whose common bile ducts can be ligated without disturbance of health 365, might show whether these animals fail to absorb cholesterol, or accumulate it in their bodies, or dispose of it by some unknown process.

b — *Renal and vascular disorders.* — Lipemia and cholesterolemia have been described by several authors 47. 61. 77. 151. 249. 372 in kidney diseases, and have been stressed by Epstein 105. 106 as a part of the picture of a certain type of nephrosis. An increase of blood cholesterol has also been described in some but by no means all cases of hypertension and arteriosclerosis. Cholesterol excess as a cause of vascular disease was suggested by the deposits of cholesterol in atheroma 1. 76 and by the results of cholesterol feeding in rabbits, and has received notice by MacCallum 250 in a recent review of arteriosclerosis. As mentioned elsewhere, such experiments are negative in carnivora and omnivora 3. 14. 65. 75. 297. 360. 361. 371. The support for such a theory is wholly inadequate, and the cholesterol in atheromatous patches is probably to be regarded as a secondary deposition, similar to what is found in other chronically damaged tissues.

(c) — *Diabetes.* — In diabetic lipemia, increase of cholesterol is more marked and protracted than that of lecithin 4. 5. 30. 58. 66. 123. 127. 138. 164. 181. 182. 262. 292. As in the case of lecithin, however, the rise does not run parallel to that of the glycerides, so that with increasing lipemia, though the absolute cholesterol values mount higher, the ratio to total fatty acids progressively falls. Contrary to the rule for lecithin, the increase of cholesterol occurs in the plasma rather than in the corpuscles 43. 58. 62. 66. 67. 140. The stubbornness of the elevation of cholesterol is remarkable 20. 43, and, as shown in the preceding paper, when an existing lipemia has been suppressed by the most rigid restriction of both fat and cholesterol in the diet, hypercholesterolemia still tends to remain as the most persistent sign of severe diabetes, and accordingly of grave prognostic import 184. According to the literature, the hypercholesterolemia of cholelithiasis, arteriosclerosis, nephritis, etc. is probably more easily amenable to reduction by diet 20. 61. 84. On the other

hand, diet may be effective in regulating blood cholesterol in milder diabetes [16], and ineffective in nephritis [47]. The increase of cholesterol following hemorrhage in rabbits appears to be persistent, at least until the blood loss has been made good. In mild diabetes the blood cholesterol is generally not increased [58, 108]. Lipemia and cholesterolemia are said not to result from hemorrhage in dogs. They occur after hemorrhage in human patients [67, 119] but are absent in primary and most secondary anemias [169]; in fact, subnormal cholesterol values are reported in pernicious anemia [46, 60, 90, 103, 136, 279] and leukemia [107]. The reason for the obstinate increase of blood cholesterol in severe diabetes and also the possible point of contact between diabetes, nephritis and hemorrhage in this respect remain entirely unknown. Increase of cholesterol in the bile, which commonly accompanies hypercholesterolemia, has been reported in diabetes [19].

d — *Experimental lipemia.* — Increase of cholesterol is characteristic of all the known forms of experimental lipemia. As mentioned, the anemic lipemia of rabbits seems chemically to resemble that of diabetes. Cholesterol holds a place of primary importance in the pathological alimentary lipemia of rabbits and guinea pigs. The earliest Russian workers produced this abnormality in rabbits by feeding such things as eggs, milk, and brain, and attributed it to the carnivorous diet [163]. Later workers demonstrated the specific rôle of chelesterol [13, 14, 22, 66, 75, 86, 265, 364]. The feeding of cholesterol-poor fats (olive oil, sunflower oil, suet) was found to produce no lipemia. Pure cholesterol added to a fat-poor diet gave slight or inconstant results, partly because of poor absorption [188, 363]. The administration of cholesterol suspended in oil produced extreme degrees of lipemia and secondary anatomic changes which proved fatal in prolonged experiments. Only herbivora, not carnivora or omnivora (dogs, rats) are subject to these lipoid accumulations in blood and organs from fat or lipoid feeding [3, 14, 66, 75, 297, 360, 361, 371].

e — *Local accumulations of cholesterol.* — Cholesterol occurring in excess in the blood is taken up by the parenchymal cells of certain organs, e.g. adrenal cortex [22, 266], corpus luteum, and certain cells of the kidneys [46, 99, 122, 194, 265, 373], and also by cells chiefly of endothelial type, classified by H. M. Evans [110, 335] as macrophages. These latter are divided into three groups, viz., true endothelial cells, lining the capillaries of the hepatic lobules [266], the capillaries and venules of the spleen, bone marrow and hemal glands, and the lymphatic sinuses of the lymphatic glands; second, more or less fixed cells in the splenic pulp [228, 266, 344] and bone marrow, wandering cells of connective tissue, etc.; and third, the free macrophages (endothelial leukocytes of Mallory) in the serous cavities, lymph sinuses of lymph glands, and in the blood [267, 321]. The Kupffer cells are supposed to pass on the cholesterol to the epithelial cells of the liver for excretion in the bile. In rabbits, the taking up of cholesterol by all the types of cells mentioned causes not only their enlargement but also their proliferation, which in many regions is followed by secondary breakdown and fibrosis. A form of cirrhosis of the liver is one result. Deposits also occur

in the large blood vessels, so that a certain imitation of atheroma and arteriosclerosis is produced [13, 14, 265, 360, 361]. Cholesterol deposits in the cornea also give rise to a typical arcus senilis [364]. As previously mentioned, all attempted applications of these results to human pathology and all hypotheses of cholesterol excess as the primary cause of diseased conditions in man have remained unproved. Chauffard[76, 78, 82, 186] set up a premature brilliant theory, linking nephritis, lipemia, cholesterol deposits in the kidneys, arteriosclerosis, retinitis, the arcus senilis and xanthelasma, through the common bond of hypercholesterolemia. It is evident, however, that all these associations are inconstant, and though cholesterol deposits characterize chronic retinitis and the arcus senilis, they are strictly secondary to the primary damage [131, 209, 372]. In local hemorrhages, exudations and inflammations, cholesterol may persist for long periods because of the difficulty of its absorption or decomposition [7, 15, 33, 176, 216, 322, 332, 355, 370]. Though the opacity of the human arcus senilis is associated with cholesterol deposit, it remains uninfluenced by diet, while the imitation of it in the rabbit is a transitory phenomenon which clears up when cholesterol feeding is stopped. The xanthoma formations of diabetes or cholelithiasis are by no means parallel to the hypercholesterolemia, and it seems obvious that some other primary factory is concerned [16, 41, 111, 328, 334]. Above all it is noteworthy that the heaviest and most prolonged lipemia and cholesterolemia in diabetes is frequently not accompanied by xanthomata or ocular troubles, creates no greater tendency to arteriosclerosis than is found in cases with trivial lipemia, and never gives rise to the organic scleroses observed in rabbits. The attempts to correlate cholesterol with tumor growth [221, 225, 226, 295, 296] have thus far remained suggestive rather than conclusive, and all investigations in the widest possible range of other diseases [100, 114, 160, 262, 282, 290, 327, 356, 357] have proved unfruitful.

Normal Standards

Normal figures for blood lipoids are hard to define exactly, because of the differences resulting from different physiological states and particularly from different methods of analysis. The findings by the older methods are reviewed by Magnus-Levy and Meyer. The newer data are based mostly upon the methods of Bang (vide papers of Bang[24, 25] and of Schlippers for results) and of Bloor. The values found for normal human blood by Feigl agree reasonably closely with those of Bloor, except that this author considers Bloor's cholesterol figures too high and sets 0.200 — 0.220 per cent as the usual normal range. Myers and collaborators[258, 259] refer to older figures, such as those of Grigaut (cholesterol of human blood 0.150 — 0.175 % in serum or plasma, 0.130 — 0.171 % in

CASE	TOTAL FATTY ACIDS %			LECITHIN %			CHOLESTEROL %			FAT %		TOT. FATTY ACIDS / LECITHIN			LECITHIN / CHOLESTEROL		
	Whole blood	Plasma	Corpuscles	Whole blood	Plasma	Corpuscles	Whole blood	Plasma	Corpuscles	Plasma	Corpuscles	Whole blood	Plasma	Corpuscles	Whole blood	Plasma	Corpuscles
Men (Bloor)																	
Normal High	0.41	0.43	0.45	0.33	0.26	0.44	0.25	0.31	0.23	0.16	0.15	1.41	1.90	1.14	1.63	1.26	2.32
Normal Average	0.36	0.38	0.36	0.30	0.22	0.40	0.21	0.22	0.19	0.11	0.07	1.20	1.68	0.89	1.44	0.96	2.08
Normal Low	0.29	0.30	0.28	0.29	0.20	0.35	0.19	0.19	0.17	0.04	0.00	0.97	1.41	0.70	1.20	0.84	1.90
Women (Bloor)																	
Normal High	0.42	0.47	0.34	0.31	0.22	0.48	0.24	0.26	0.24	0.20	0.03	1.45	2.70	0.77	1.33	0.95	2.60
Normal Average	0.36	0.40	0.29	0.29	0.19	0.44	0.23	0.24	0.21	0.16	0.01	1.31	2.15	0.69	1.29	0.82	2.14
Normal Low	0.32	0.35	0.27	0.28	0.17	0.39	0.21	0.21	0.19	0.12	0.00	1.20	1.86	0.63	1.29	0.75	1.80
Dog (Bloor)	0.52			0.33			0.17					1.58			1.90		
Rabbits (Horiuchi)																	
Diets of																	
Carrots	0.28	0.22	0.36	0.21	0.10	0.40	0.10	0.06	0.16			1.34	2.19	0.91	2.10	1.82	2.52
Sunflower Seed	0.34	0.30	0.42	0.21	0.11	0.38	0.11	0.07	0.18			1.70	2.93	1.13	1.92	1.53	2.22

corpuscles), and in their own observations find percentages closer to those of the older authors than to those of Bloor. (Cf. also Rosenthal[311, 312] and Schnable[327]). With allowance for this discrepancy, the following table summarizes the values for blood lipoids which are now generally accepted as normal.

Experiments *

The writer was chiefly interested in experiments to produce lipemia, thus adding one more point of identity between clinical and experimental diabetes, and in attempts to find the cause or determining factor for the excess of circulating fat. The much larger task of the chemical analyses and the finer details of relations between the different lipoids was undertaken by Miss Mary B. Wishart. Over fifteen thousand samples were taken for these analyses, this large number not representing superfluity or repetitions, as consideration of the problem will show. Each specimen of blood as a rule was analyzed in three parts, viz., whole blood, plasma and corpuscles, as a means of checking the results. Each of these fractions was analyzed separately for total fat, lecithin and cholesterol. Determinations of the cholesterol esters were planned but never performed. The numerous lines of investigation necessary for judgment of the possible factors suggesting themselves are indicated in the ensuing summary.

The protocols of most of these experiments are given in connection with other subjects, mostly in the series of papers to be published concerning acidosis. The lipemia investigation thus required no extra animal experiments beyond a few normal and other controls. As the production and management of such diabetic states is tedious, it is a decided saving of labor to use the same animal for an entire range of clinical, chemical and pathological observations, and the greatest advantage of all is found in the completeness of the picture thus obtained, so that each group of phenomena can be followed intelligently in its relations to the other groups. This plan of investigation encountered obstacles and was carried out only with great difficulties, but approximately ten thousand of the lipoid analyses mentioned were completed. These were expected to

* Performed in the Hospital of the Rockefeller Institute for Medical Reserach, New York; 1915-1917.

furnish material for a long series of papers on lipemia, to be published chiefly by Miss Wishart, most of whose time for over two years was devoted to this work. In the several changes of residence made necessary by the war, all the notebooks containing the results of the lipoid analyses were lost, and nothing was saved except the few tables presented in the preceding article, which happened to be preserved among some loose papers. The greater part of this work was thus lost altogether, and the proposed series became curtailed to two papers. In particular, the finer details of the lipoid chemistry had never been brought together and studied for such light as they might shed upon normal or pathological fat metabolism, and there is nothing to show for the labor devoted to this side of the problem. On the other hand, the production of lipemia is a simpler matter, and the results in this part of the problem can be stated from the animal protocols, and will therefore be outlined in general terms under the following heads:

(1). Lipemia in diabetic dogs.

The following is a single typical example of many observed.

Dog C 3-27.—Female, mongrel, yellow, age 4 years, excellent nutrition. Weight 16.25 kg. July 8, 1915, removal of pancreatic tissue weighing 34.0 gm.; remnant about main duct estimated at 4.4 gm. (about 1/9). Glycosuria ensued on bread feeling, but was absent on meat. The dog thrived and was kept in a borderline condition on protein-fat diet, until by the first of March, 1916 the weight had risen to 21 kg. Notwithstanding this obesity, it was found that the feeding of bread even with addition of as much as 300 gm. of glucose daily no longer produced glycosuria. Regeneration in the pancreas remnant had brought an apparent cure of the diabetes, to such an extent that this heavy functional strain could be borne without apparent harm. Therefore, on March 9, 0.9 gm. of pancreatic tissue was removed from the remnant and was found microscopically normal, without hydropic or other changes. Bread feeding then failed to produce glycosuria, but with addition of 200 gm. of glucose glycosuria was heavy and continuous. It then persisted with gradual reduction of carbohydrate, until the diet on April 8 became 200 gm. beef lung, 200 gm. suet, and 100 gm. bread. Both acidosis and lipemia became heavy, while the body weight remained at 19 or 18 kg. The blood plasma had the appearance of heavy cream, and contained over 15 % of total fat. Coma death occurred April 22, with lipemia still heavy.

In a previous publication[8], brief records were given of dogs (Tables I, V, VI) with severe diabetes on high fat diets, with little or no lipemia. Numerous observations made it evident

that conditions in dogs fully resemble those in human beings, inasmuch as some patients and some animals develop intense lipemia, as in the above example, while the majority of patients and animals under seemingly identical circumstances have clear blood plasma and comparatively low lipoid analyses. In one sense such a sharp contrast does not exist, because every patient and animal with severe diabetes shows more or less elevation of fat and cholesterol in the blood, unless this is prevented by dietary restrictions or cachexia; also, milder degrees of lipemia are more common than the intense form, and every grade of transition is thus found between the smallest and the largest accumulations of circulating lipoids. Nevertheless, the fact remains that the individual variations are very wide, and ample experimental opportunities are afforded for testing supposed etiologic factors, first by attempting to produce heavy lipemia in animals having little spontaneous tendency to it, and second by trying to reduce lipemia in animals in which it is already heavy. In this way a number of influences were tested, and definite though mostly negative results obtained.

(2). Etiologic Influences Tested.

A.—Positive.

(a) *Active diabetic Symptoms.*—The basic etiologic condition found was active severe diabetes. Milder grades of diabetes were never attended with marked lipemia, regardless of diet. Any intense lipemia was quickly abolished by any dietetic or other measures which controlled glycosuria even temporarily. Recent authors[30, 44, 45, 62, 84, 85] have found that diabetic patients on high fat diets do not always exhibit heavy lipemia, and when such diets abolish glycosuria an existing lipemia may at the same time markedly diminish. Such observations fully parallel those made in dogs. The reduction of lipemia affords no evidence that a given diet is suitable for prolonged control of the diabetes, and the fact that this reduction may sometimes be accomplished by reduction of carbohydrate and increase of fat in the diet is in no way paradoxical, but conforms fully to the rule governing lipemia. If the high fat diets finally lead to a return of glycosuria, heavy lipemia may then

return. Unskillful use of fasting may sometimes increase lipemia as well as acidosis[85], but no doubt is thus cast upon the benefits of fasting and fat-free diets, when properly employed, for controlling these and other diabetic symptoms[58, 62, 138].

(b) *Diet.*—The requirements for a diet to produce lipemia are merely that it shall maintain active diabetic symptoms and shall supply a considerable quantity of fat. Carbohydrate in no way interferes with the production of lipemia, and there is no specific influence of protein. Attempts to force too high a ration of fat at the expense of reduced carbohydrate and protein defeat their own purpose by spoiling the appetite or the digestion of fat and thus leading either to a subsidence of diabetic symptoms or to cachexia. For practical purposes the most successful diet has been a well-balanced mixture of protein, carbohydrate and fat, merely because such a mixture gives the best and longest preservation of appetite, digestion, and general well-being. Approximately equal parts by weight of lean meat, bread and suet have proved serviceable, with changes to suit the preference of the individual dog, and usually with the addition of considerable bone meal or talcum powder to prevent diarrhea. Repeated and determined attempts were made to produce lipemia on the assumption that it might be the rsult of prolonged excess of fat or a preponderance of fat over carbohydrate or protein in the diet. One-sided fat diets were thus pushed to the point of producing peculiar fatal disturbances, to be described in detail later, but no significant grade of lipemia resulted in normal dogs, partially depancreatized non-diabetic dogs, or diabetic dogs free from glycosuria. The kind of fat was also not a determining factor.

(c) *Individual idiosyncrasy.*—The observed differences between individual patients and animals can only be classed under this vague title. At the time of these experiments, the writer was not aware of the differences between normal dogs in susceptibility to lipemia, as described by Bang[26], and the loss of the chemical analyses prevented such observations in the normal controls used. It seems a plausible assumption that the normal dogs which are most subject to alimentary lipemia are also the ones which develop the most marked lipemia after becoming diabetic, and the hypothesis is well

worth experimental trial. There is likewise the possibility that such differences in fat assimilation exist between different normal persons, and that exaggeration of these differences under a pathological metabolic strain accounts for the individual variations in diabetic lipemia. These assumptions, if found correct, nevertheless fail to explain the fundamental cause of the differences in fat metabolism among either normal or diabetic individuals.

B. — Negative.

(a) *Direct endocrine influence of the pancreas.*—The endocrine function of the alpha cells of the islands and perhaps other elements of the pancreatic parenchyma remains unknown. A possible hypothesis might be that pure diabetes results from deficiency of the beta cells of the islands, and that slight or heavy lipemia may be added as the result of slight or severe damage of certain other pancreatic cells. Three groups of animals are available for a test, viz., totally depancreatized dogs, dogs with severe diabetes due to small size of their pancreas remnants, and dogs with large or hypertrophic pancreas remnants but with severe diabetes brought on by overfeeding or transitory inflammation, or both[9, 10, 11]. The result of carbohydrate overfeeding is a specific degeneration and loss of the beta cells, leaving the other elements of the pancreas usually intact. Heavy lipemia has rarely been described in totally depancreatized animals[31, 33], but as fat digestion is practically abolished in such animals the only possible source of such a lipemia must be from the body fat, and there is reason to believe that the chief origin of diabetic lipemia is from the food fat. The comparatively negative findings in totally depancreatized dogs are therefore not conclusive. No differences in susceptibility to lipemia have been observed between dogs with small and large pancreatic remnants, except that digestion of fat is usually less efficient in the former. On the whole, diabetic dogs with the largest possible pancreatic remnants are best suited for the production of lipemia, because they are best able to digest fat. As these animals also are most liberally equipped with alpha and other pancreatic cells, and are deficient in their beta cells alone, their equal or greater susceptibility as compared with dogs with small pan-

creatic remnants renders it highly improbable that deficiency of the alpha or other unknown cells is responsible for lipemia. Furthermore, careful microscopic studies of the pancreatic remnants of a long series of diabetic dogs, with and without marked lipemia, has revealed no changes in any cells which could be considered as either the cause or the effect of the lipemia.

(b) *Liver.*—As the liver is considered to be the main central station of fat metabolism, the conjecture is possible that the different degrees of lipemic tendency may represent different degrees of liver efficiency in carrying the increased burden of fat metabolism associated with diabetes. Several groups of experiments were performed, viz., with removal of one-third to one-half of the liver, with the Eck fistula, and with removal of the left kidney and suture of its artery to a branch of the splenic vein so as to send a strong current of arterial blood through the liver. Such arterio-venous anastomoses generally became thrombosed in the course of a few days, and none of the animals with Eck fistula or liver resection possessed a sufficient combination of vitality and fat digesting ability to be entirely satisfactory for lipemia experiments after becoming diabetic. No very powerful influence of the liver deficiency was manifest, however, as none of these animals developed lipemia.

(c) *Adrenals.*—Several dogs before or after being made diabetic were subjected to removal of the entire right adrenal and two-thirds or three-fourths of the left. According to the reports concerning rabbits, this condition should dispose to an increase of blood cholesterol. The finer analytical results are lacking as usual, but none of these animals developed any marked lipemia. Adrenal deficiency, therefore, seems to be not a factor in diabetic lipemia. Also, subcutaneous or intraperitoneal injections of epinephrin failed to produce lipemia in diabetic animals.

(d) *Thyroid.*—Experiments with thyroid feeding and with thyroidectomy in partially depancreatized animals have been previously described[12]. The results of the blood fat analyses in these experiments were lost, but no marked effect as regards lipemia was observed.

(e) *Sex glands.*—No differences in lipemia were observed

between male and female animals. Removal of ovaries or testes also had no apparent influence.

(f) *Species.*—Diabetes has been produced in cats and several other mammalian species, as described in another series of papers, but accidentally or otherwise lipemia has been missed in these species. The literature of diabetes in birds and cold-blooded animals also contains no mention of visible lipemia. It should be noticed, however, that total pancreatectomy rarely produces marked lipemia even in the dog, and few species can digest high fat diets for as long a time as the dog during the severe stage of the diabetes following partial pancreatectomy. Fatty liver is commonly found in the above species.

(g) *Age.*—No differences of lipemic tendency have been observed between young and old animals.

(h) *Degree of hyperglycemia and glycosuria.*—Heavy lipemia in diabetic patients or animals is regularly attended by intense glycosuria and hyperglycemia, but the lack of parallelism between the sugar and fat analyses, as reported by former authors[31, 138], is confirmed.

(i) *Acidosis.*—Nearly every case of acidosis is attended with at least a slight lipemia, and heavy lipemia is practically never found except in connection with some degree of acidosis. This is merely a different statement of the fact that severe diabetes is practically always attended with some degree of lipemia, and that the heaviest lipemia occurs only in severe active cases on high fat diet, which naturally gives rise to acidosis. No parallelism exists between the degree of lipemia and the degree of acidosis as measured either by the acetone of blood or urine or the CO_2 capacity of the blood plasma[4, 30, 58, 61, 62, 97, 138]. On the contrary, discrepancies are very marked, for many cases go on to coma with nearly or quite clear plasma and relatively low fat analyses, while other cases show heavy lipemia with much slighter grades of acidosis. The notion of lipemic embolism as the cause of coma has never had any sound basis[142, 149, 264]. It is worthy of notice that though lipemia and acidosis represent defects in fat metabolism at different stages, neither of them exhibits the slightest etiologic relationship to the other.

These statements referring to acidosis have held good also in a wide range of experiments with artificial forms of acidosis,

produced by injections of hydrochloric acid, phosphoric acid, acid sodium phosphate and a series of lower fatty acids, as described in the forthcoming series of papers on acidosis. None of these substances has produced lipemia in normal or diabetic animals, or caused reduction of an existing lipemia unless by reason of mere cachexia.

(j) *Alkali.*—The administration of small or large doses of sodium bicarbonate or carbonate, by mouth or intravenously, has caused no specific change in the tendency to lipemia.

(k) *Others salts.*—Oral, intramuscular or intravenous administration of sub-lethal doses of potassium or calcium chloride, or magnesium sulphate, on single days or continued daily for several weeks, have had no apparent influence upon lipemia. Phosphate injections have had no perceptible effect outside of disturbances of the general health. These tests were suggested by the possible relationship between these inorganic substances and fat metabolism.

(l) *Fats in the diet.*—The more fluid forms such as olive, cottonseed and other oils are inconvenient from a practical standpoint because of their greater tendency to produce diarrhea. The heavier fat of suet, though theoretically less readily digested, serves the practical purpose better. Lard, butter and cream have sometimes been substituted experimentally or to promote appetite by relieving the monotony of the diet, with no difference as regards the lipemic tendency. The feeding of stearic or oleic acid for short periods has had no apparent influence except in connection with their greater difficulty of digestion.

(m) *Cholesterol.*—Various quantities of various emulsions of cholesterol were injected intravenously, occasionally with fatal results, and no special effects were observed from the smaller doses which could be given safely in this way. Cholesterol feeding was used on a larger scale, sometimes in the form of pure cholesterol in doses up to 5 gm. daily, and more often in the form of diets composed largely of brains or egg yolks. This investigation seemed specially promising as an attempt to correlate the different known forms of lipemia. It is noticeable that the earliest known experimental lipemia, viz., that of stuffed geese, was produced not by neutral fat but by a grain diet in which vegetable sterols may have a possible importance[52]. As above menetioned, the alimentary lipemia of

rabbits or guinea pigs is produced by feeding cholesterol with fat. In anemic rabbits cholesterol is somehow mobilized from the tissues, and therefore may be concerned in the production of the lipemia. Furthermore, as above noted, cholesterol accumulation is not only a prominent feature of clinical and experimental diabetic lipemia, and likewise of nephritic and other lipemias, but it also appears to be the most stubbornly persistent feature. It therefore seemed a plausible hypothesis that while normal human beings and dogs are resistant to any intense alimentary lipemia, their metabolism might be weakened by diabetes so as to reduce them to somewhat the same level of susceptibility as rabbits. Differences in lipemic tendencies might then be explained partly perhaps by an unknown individual predisposition, but partly also by differences in the cholesterol content of the diet. The available information does not fully settle this question. The finer details of the blood changes were lost with the loss of the analytical figures, and data of the fecal analyses which were made are also necessary to establish the amount of cholesterol absorption. In a broad sense, however, this investigation was negative as an attempt to explain diabetic lipemia. None of the resistant classes of dogs (normal dogs, partially depancreatized non-diabetic dogs, diabetic dogs free from glycosuria, or dogs with active diabetes and little spontaneous tendency to lipemia) developed any obvious heavy lipemia on cholesterol feeding. On the other hand, widely different tendencies to lipemia are found in different patients and animals on identical diets.

(n) *Lecithin.*—The information concerning lecithin in the alimentary lipemia of rabbits is that it does not give rise to lipemia or organic degenerations when fed alone or with neutral fat, but does not interfere with these changes as produced by the feeding of fat and cholesterol. Two kinds of lecithin were used in these experiments on dogs, viz., a commercial product said to be made from brains, and some egg lecithin kindly supplied by Dr. West of the chemistry department of the Rockefeller Institute. The feeding of such lecithin for longer or shorter periods produced no obvious increase or decrease of lipemic tendency in diabetic or non-diabetic dogs, though nothing can be said concerning possible minor changes in the blood lipoids. Intravenous lecithin injections also failed

to cause any marked lipemia in non-lipemic animals or to reduce appreciably any existing lipemia.

In contrast to the rule for other fatty substances, such large quantities of lecithin can be given by fairly rapid intravenous injection as to give rise to distinct cloudiness in the plasma and a scum on centrifugalization. For example, on April 3, 1917, 26 gm. of egg lecithin was rubbed up in a mortar with water to a total volume of 300 cc. The addition of 1 gm. sodium carbonate cleared up this turbid mixture to a convenient consistency. Portions of 100 cc. each were injected into 3 dogs of approximately 10 kg. wt., viz., one normal, one phlorizinized, and one totally depancreatized animal, the time occupied for each dog being from 10:30 to 11:30 A.M. No symptoms resulted in either the normal or the diabetic dog. No symptoms followed immediately upon the injection in the phlorizinized dog, but during the ensuing four or five hours the animal developed weakness almost to the point of unconsciousness, with polyuria and involuntary urination and defecation. Gradual recovery then occurred, but the animal was in a drunken and dazed condition for the remainder of the day. By evening she showed appetite, but had difficulty in chewing and swallowing meat. The next morning the condition was normal. The disappearance of turbidity in the plasma and the scum after centrifuging occurred rapidly with all the animals, viz., within an hour, but seemed to be slower in the depancreatized dog than in the other two. The analyses for cholesterol were saved in this experiment, and showed that the cholesterol of both plasma and corpuscles remained unchanged by the lecithin injections.

The ability to give considerable quantities of lecithin intravenously may have possible interest for parenteral feeding purposes. If lecithin is the metabolic form of fat it should be well suited for this use, and as it mixes with glucose it might be employed to enhance the caloric value of glucose solutions. The chance of any harmful results will naturally require study.

(o) *Nutritive state.*—It might be anticipated that obese animals would be most disposed to lipemia, also that total pancreatectomy in a very obese dog might give rise to heavy lipemia. These suppositions were found contrary to fact. No high grade of lipemia was observed after total pancreatectomy, though the operation was performed upon a series of enormously obese dogs with a view to both lipemia and acidosis.

As digestion and general well-being are important factors, it is well not to attempt to produce lipemia in dogs immediately after partial pancreatectomy, but to allow several weeks or even months for recovery on a diet which keeps glycosuria absent. For this reason some of the best results were obtained in animals used for experiments with high fat diets, which gradually brought on obesity and with it an outbreak of diabetic symptoms. The same results, however, are obtained with other kinds of preliminary diets so long as the animals are kept strong and well, and thin dogs seem to be as easily subject to diabetic lipemia as the obese ones. Clinical conditions in this respect are parallel, for it is well known that the heaviest lipemia is often found in the most emaciated patients.

(p) *Anemia.*—No experiments were performed with single large hemorrhages in severely diabetic dogs. So many blood samples were taken for analyses from some of these animals that they became moderately anemic, but no special lipemic tendency resulted. Bloor[62] and Gray have mentioned a "false anemia" in clinical cases of heavy diabetic lipemia, which disappears when the lipemia clears up. Apparently no studies of blood volume have ever been made, but when twenty per cent (more or less) of fat accumulates in the blood in a severe case, it is conceivable that the blood volume may be increased and the corpuscle and hemoglobin percentages reduced in some such proportion.

(q) *Exercise.*—Muscular exercise may slightly increase the blood fat of normal dogs, but heavy labor on the treadmill has produced no perceptible change in the lipemic tendency of diabetic dogs.

(r) *Vitamines.*—Butter is on a par with other fats, as above mentioned, and the feeding of yeast has had no perceptible influence upon diabetic lipemia.

(s) *Levulose.*—Feeding or subcutaneous injection of levulose produced no apparent reduction of existing lipemia in diabetic dogs.

(t) *Phlorizin.*—One of the easiest suppositions is that the burden of fat metabolism resulting from the simple loss of sugar from the body creates the tendency to lipemia. The utmost effort was therefore made to produce lipemia in dogs receiving various doses of phlorizin. Some animals with total D : N ratios and acidosis were fed only pure fat for about a

week. Others receiving smaller doses of phlorizin were used as controls for diabetic dogs on the identical diets, for as long as three months continuously. Though phlorizination together with protein-fat diet can thus maintain a close imitation of diabetes in respect to both glycosuria and acidosis for long periods, no heavy lipemia such as observed in many diabetic dogs was ever found in any of the phlorizinized dogs.

In various other series of experiments connected with this diabetic research several hundred blood samples have been taken from dogs receiving various doses of phlorizin while fasting, or on various diets, and no appearance like diabetic lipemia has ever been seen. A slight increase of blood fat, presumably due to the loss of sugar and increase of fat metabolism, has been described in phlorizin poisoning, but the entire literature of this condition contains no mention of lipemia of the degree which is familiar in diabetes. The statement is therefore justified that hyperlipemia in the diabetic sense never occurs in phlorizinized animals. This fact is the more remarkable because the fattiness of the liver, kidneys and other organs is fully as great in phlorizin poisoning as ever found in diabetes. The observations furnish another point of difference between phlorizin poisoning and diabetes, and prove that lipemia is not due merely to loss of sugar from the body.

Conclusions

1. Severely diabetic dogs which digest high fat diets regularly develop some degree of abnormal lipemia, and in a minority of such animals this lipemia becomes extreme (15 % or more of blood fat). It is known that the chemical peculiarities as respects the relations of neutral fat, cholesterol, lecithin, etc. resemble those in human diabetic lipemia, though the great mass of the analytical results were lost. The chief positive result of this investigation therefore is the establishment of a complete similarity between clinical and experimental diabetes in regard to lipemia.

2. Apart from a sufficient supply of fat in the diet, the one indispensable prerequisite for diabetic lipemia is the existence of active severe symptoms in the form of glycosuria and hyperglycemia. Mild cases with high glycosuria and severe cases

with glycosuria abolished by diet never exhibit any extreme grade of lipemia, however high the fat intake.

3. Diabetic lipemia evidently represents some secondary breakdown in fat metabolism, not directly connected with the endocrine function of the pancreas and not due merely to excess of fat in metabolism or loss of sugar from the body. There are wide variations in individual susceptibility to this disorder among both animals and patients. Tests with a wide variety of endocrine, dietary and other influences failed to reveal the nature of the disturbance or the origin of the susceptibility.

Bibliography and Abstracts

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2.—Adler, H. M. Unsaturated fatty acid as a neurolytic agent, *J. Amer. Med. Assn.*, 59, 1912, 219-220. Hemorrhage and destruction of nerve cells resulted from intracerebral injection of oleic acid but not of triolein in cats.

3.—Adler, L., Studies in experimental atherosclerosis. A preliminary report. *J. Exp. Med.*, 20, 1914, 93-107. Prolonged feedings or injections of various substances in the attempt to produce atherosclerosis in dog. In the list were cottonseed oil (50 cc. daily) and cholesterol (0.5 gm. every other day). These gave slight atherosclerotic changes, together with elevated blood cholesterol in all normal dogs, but one poisoned with uranium showed unexpected resistance to this change. Extensive deposits of cholesterol in organs as described in rabbits were not found in dogs.

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klin. Woch., 47, 1910, 1323-4. Further emphasis of dominant role of cholesterol.

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12.—Allen, Frederick M. Experimental studies in diabetes: Series II. 10. The influence of the thyroid upon diabetes. *J. Metabol. Res.*, 1, 1922, 619-665.

13.—Anitschkow, N. Die pathologischen Veränderungen innerer Organe bei experimenteller Cholesterinesterverfettung. *Dtsch. med. Woch.*, 39, 1913, 741-743. Earlier results from feeding rabbits with egg-yolk, etc., are shown to be due to cholesterol. The cholesterol-loaded Kupffer cells go to pieces and are replaced by fibrosis, imitating ordinary cirrhosis resulting from destruction of liver cells. Changes in the aorta are described in detail and pronounced similar to human atherosclerosis. The spleen, bone marrow, and lymph nodes contain enormous quantities of anisotropic "liquid crystals" of cholesterol esters in phagocytic cells. The lipochrome also present is considered a decomposition product of cholesterol.

14.—Anitschkow, N., and Chalatow, S. Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischen Prozesse. *Centrallb. f. allg. Path. u. path. Anat.*, 24, 1913, 1-9. Oil feeding alone proved negative, but addition of cholesterol caused lipoid deposits in organs, also anisotropic droplets in the blood serum. The bile was extremely rich in cholesterol. Rabbits and guinea pigs were susceptible to the pathologic changes, but rats were resistant.

15.—Arndt, W. Ueber das physiologische und pathologische Vor-

kommen morphologisch darstellbarer Lipoide in den Geschlechtsorganen des Weibes, *Monatsschr. f. Geburtsh. u. Gynaek.*, 49, 1919, 315 and 413. Considers lipoids important as activators, kinases, inhibitory agents, and in reaction to toxins. Reviews literature of morphology of fat in female sex organs. Lipoids in the uterus increase with age. Elsewhere they are found only in blood vessel walls, and especially in the Fallopian tubes with acute or chronic inflammations. They are then formed in the tube wall itself, in addition to being absorbed from the contents.

16.—Arning, E., and Lippmann, A. Essentielle Cholesterinämie mit Xanthombildung. *Ztschr. klin. Med.*, 89, 1920, 107-119. Xanthomata contain cells loaded with cholesterol, and occur chiefly secondarily in diseases with hypercholesterolemia, such as icterus or diabetes. Diabetic xanthomata often disappear when sugar is reduced. One case is described in a diabetic, also one so-called "essential" case, because cholesterolemia and xanthomata were present without diabetes or other known cause. The blood cholesterol could be reduced by restriction of the intake, and raised by cholesterol feeding in quantities of one or two gm. daily without high fat intake. The high blood cholesterol continuing as long as 5 days after a single dose of 3 or 5 gm. was taken to indicate impaired cholesterol excretion. Xanthomata are considered to represent secondary deposits of cholesterol in tissues having an affinity for it, rather than as primary fibromata which become saturated with cholesterol.

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19.—Bacmeister. Untersuchungen über Cholesterinausscheidung in menschlichen Gallen., *Biochem. Ztsch.*, 26, 1910, 223-230. Analyses of human bile gave some indication that the cholesterol content was higher in a diabetic than in three non-diabetics.

20.—Bacmeister (Discussion) *Verh. d. dtsch. Kong. f. inn. Med.*, 30, 1913, 177. In non-diabetic cases of hypercholesterolemia (arteriosclerosis, uremia, etc.) the cholesterol percentage falls before death. Only with diabetes is there an increase of blood cholesterol persisting up to death, even apart from diabetic coma.

21.—Bacmeister and Henes. Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Erkrankungen. *Dtsch. med. Woch.*, 39, 1913, 544-546. Blood cholesterol was found low with cholesterol-poor diet, old age, emaciation, bad general health and especially any rise in temperature, and high with cholesterol-rich diet, typhoid fever, and all severe

metabolic disorders (diabetes, obesity, nephritis, recent arteriosclerosis).

22.—Bailey, C. H. Atheroma and other lesions produced in rabbits by cholesterol feeding. *Jour. Exp. Med.*, 23, 1916, 69-85. Fed nine rabbits on egg yolk and six on pure cholesterol in oil (usually 0.5 gm. in 10 cc.; one control received cottonseed oil without cholesterol). The adrenal cortex was enlarged by anisotropic deposits. Aortic atheroma resembled human atherosclerosis in appearance and course, and lesions were found in the pulmonary and other vessels. Large deposits of anisotropic fat in the liver led to cirrhosis, and in some rabbits similar lesions occurred in the kidneys.

23.—Bang I. *Chemie und Biochemie der Lipoide*, Wiesbaden, 1911, General compend. One suggestion is that lipoids influence ferment activity in the liver.

24.—Bang, I. Ueber Lipoidämie, I. *Biochem. Ztsch.*, 90, 1918, 383-387. He calls earlier figures for blood lipoids worthless. With his new method he fixes the norm for human subjects from seven weeks to seventy-eight years of age, as follows: "fat" 0.0-0.35%; cholesterol 0.07 — 0.125%; "alcohol fraction" (interpreted as fatty acids) 0.24 — 0.39%; esters 0.12 — 0.20%; phosphatids 0.13 — 0.27%. For normal dogs the percentages are: "fat" 0.01 — 0.05; cholesterol 0.06 — 0.145; "alcohol fraction" 0.15 — 0.41%; esters 0.07 — 0.221; phosphatids 0.17 — 0.39. Neutral fat is found only in plasma. Plasma contains much less cholesterol, but much more cholesterol esters than the cells. (The existence of esters in the red cells is evidently regarded as real).

25.—Bang, I. Ueber Lipämie. II. *Biochem Ztsch.*, 91, 1918, 104-110. Blood fat during fasting may be found either increased or decreased in the same or different dogs. Other lipoids show only insignificant variations. Feeding of butter or olive oil alone or with meat increases blood fat perceptibly in one hour, and the maximum is reached in two or three hours, or later with large doses. The increase is mostly of neutral fat; a rise of cholesterol is exceptional. Increase of the alcohol fraction, occasionally found, is not due to cholesterol esters but probably to phosphatids. Slight increase of blood fat is likewise found in human subjects after fat ingestion. Rabbits show no hyperlipemia even after abundant fat feeding and are therefore unsuitable for such experiments.

26.—Bang, I. Ueber Lipämie. III. *Biochem Ztsch.*, 91, 1918, 111-121. Investigation of conditions governing lipemia after fat feeding. Lard caused no lipemia, butter often, olive oil always, when quantities were sufficient. Habituation to fat diet reduced lipemia in both dogs and man. An influence of season, quality of food, etc., was also observed. Feeding of meat or bread alone did not alter lipemia, but when given with fat, carbohydrate strongly inhibits alimentary lipemia, supposedly through improved liver function. Fatty acids alone cause little or no increase of

blood fat, but fatty acids fed with glycerin give same result as neutral fat. Synthesis of neutral fat is thus demonstrated as a physiological process; but glycerin is indispensable, contrary to old idea of fat absorption. Criticism of opposed results of Munk and others. Also the alcohol fraction is not increased by feeding fatty acids alone. As they are probably absorbed as completely and even more rapidly than neutral fat, a transport to liver and retention in it is assumed. Individual variations also exist between animals of the same species. Animals having highest lipoids from fat feeding also seem most strongly affected by it.

27.—Bang, I. Ueber Lipämie. IV. *Biochem. Ztschr.*, 91, 1918, 224-234. Ether only exceptionally causes lipemia in dogs or rabbits. Alcohol causes lipemia in well nourished rabbits, sometimes of marked degree, but scarcely any in fasting rabbits. No increase occurs in dogs, even after preliminary fat feeding. Phosphorus in oil, producing fatty liver, never causes increase of petroleum ether extract, and cholesterol is probably decreased in blood. This also occurred in a dog with prolonged P poisoning. Cholesterol esters fell low and later rose. Phosphatids rose at first and later fell. This was also true of phosphatids in a more severely poisoned dog, in which there was a slight hyperlipemia with little change in cholesterol. With phlorizin, there was in rabbits a transitory elevation of petroleum ether extract in only one case, and in dogs, never.

28.—Bang, I. Verfahren zur titrimetrischen Mikrobestimmung der Lipoidstoffe. *Biochem Ztschr.*, 91, 1918, 86-103. Extraction principles adapted to micro methods.

29.—Bang, I. Ueber Cholesterinämie. *Biochem. Ztschr.*, 91, 1918, 122-125. Blood cholesterol is generally unchanged after fat ingestion. The slight occasional increase must come from the cholesterol taken with the diet. Bread or meat alone does not affect blood cholesterol, likewise cholesterol fed in pure form with bread or with meat. Feeding of cholesterol with fat increases blood cholesterol rapidly; after a few hours of elevation, it returns to original level. The content of cholesterol esters remains unchanged. Pathologic hypercholesterolemia was found as a constant symptom of chronic and subchronic icterus from closure of bile duct, irrespective whether this resulted from gallstones or carcinoma. Cholesterol enters blood in every long-standing bile stasis, but not as quickly as the bile pigment. In catarrhal icterus there is no hypercholesterolemia. With a cholesterol content of 2 to 10% of the dry weight of the blood, the serum showed no macroscopic abnormality, in particular no opalescence.

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carbohydrate assimilation and lipemia. Sugar ingestion inhibited lipemia, but when sugar could not be assimilated a series of three fast-days, raising the tolerance, reduced the lipemia. Hypercholesterolemia was found rarer than lipemia, and the cholesterol in most cases was normal. Phosphatids were sometimes twice normal, but showed no parallelism with diet or degree of lipemia. There was no uniform relation of lipemia to either hyperglycemia or acidosis.

31.—Bang, I. Blutuntersuchungen an pancreadiabetischen Hunden. *Lund* 1918. *Lunds Univ. Arsskr.* 1918, *n. f., avd.* 2, *bd.* 14, No. 6, 1-12. (Not available in original).

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36.—Baskoff, A. Ueber Lecithinglykose in Vergleich zum Jecorin der Pferdeleber. *Ztschr. f. physiol. Chem.*, 61, 1909, 426-53. Mixture of lecithin and glucose renders the latter partly ether soluble and the former partly ether insoluble.

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39.—Barczeller, L. Ueber den Fettgehalt der Blutes bei der Narkose. *Biochem Ztschr.*, 90, 1918, 288-289. Slight elevations of blood fat after one hour of ether narcosis of fasting dogs.

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J. Biol. Chem., 35, 1918, 15-18. By a modification of Hene's method, serum cholesterol was found as low as 70 mg. per 100 cc. in pulmonary tuberculosis. In diabetes the range was 200 to 250 mg.; in acute nephritis 150 mg., in chronic nephritis 250 to 375 mg.; in cholelithiasis 176 to 273 mg. Variable figures in other diseases.

41.—Bettmann. Die Hautkrankheiten der Diabetiker. *Dtsch. med. Woch.*, 39, 1913, 1188-94. Xanthoma is regarded as based upon cholesterolemia. The cause of the frequent skin complications of diabetes is unknown.

42.—Beumer, H. and Bürger, M. Beiträge zur Chemie des Blutes in Krankheiten mit besonderer Berücksichtigung der Lipoide. III. *Ztschr. exp. Path. u. Ther.*, 13, 1913, 343-361. Blood analyses in various diseases. Lecithin content of corpuscles is found variable in pernicious anemia, and the serum watery and reduced in proteins and lipoids. The blood fat in an inanition case with empty fat depots was low. In cachexia the corpuscles were found to suffer in number and composition, while the serum was less affected. The blood fat was increased in a case of leukemia. Icterus was found accompanied by hypercholesterolemia, and the serum might contain as much as 2.2% total fat, while appearing perfectly clear.

43.—Beumer, H. and Bürger, M. Beitrage zur Chemie des Blutes in Krankheiten mit besonderer Berücksichtizung der Lipoide. IV. Diabetes und Lipämie. *Ztschr. exp. Path. u. Ther.*, 13, 1913, 362-366. Lipemia was found present in five of seven diabetics, but absent in one youthful case and one patient dead from coma. One case of mild diabetes exhibited lipemia without acidosis. The blood cholesterol in one case remained three times normal after an oat cure had cleared up both acidosis and lipemia. In alimentary lipemia the turbidity is cleared by ether, but in pathological lipemia there is a protein-fat complex which is not cleared by simple ether extraction. The cholesterol present was mostly in free form. No lipase was demonstrable in the blood. The lipoid content of the corpuscles was little altered in spite of fat-rich serum.

44.—Beumer, H. Ueber den Cholesterinstoffwechsel beim Brustkind und den Cholesteringehalt des Serums bei verschiedenen Krankheiten. *Monatschr. f. Kinderh.*, 15, 1918-19, 581-589. Serum cholesterol of infants ranged from 0.033 (alimentary intoxication) to 0.200 percent (eczema of head in overfed breast child). There is a reduction of serum cholesterol in anemia, tuberculosis and alimentary intoxication, and an increase in icterus, and no changes in most diseases. A negative cholesterol balance was demonstrated in two nursing infants. There was no relation of serum cholesterol to exudative diathesis or rickets, and no explanation of the benefit of codliver oil by its content of cholesterol-like substances.

45.—Beumer, H. Zur pathogenetischen Bedeutung der Olsäure bei

Anämien. *Biochem. Ztschr.*, 95, 1919, 239-248. Three young puppies were fed 20 gm. oleic acid daily for four months, without lasting injury and without increase of blood cholesterol. The suggestion that oleic acid is responsible for clinical anemias is overthrown.

46.—Beumer, H. Ueber die Verteilung des Cholesterins in einigen Organen bei Nephrose und Nephritis im Kindesalter. *Monatschr. f. Kinderh.*, 18, 1920, 443-453. Damage of kindney is indicated by accumulation not of neutral fat but of anisotropic material. Four normal kidneys ranged in cholesterol content from 0.102 to 0.282 percent. In a case of hemorrhagic nephritis the kidneys contained 0.271 percent total cholesterol, against 0.314 percent in the serum. In another hemorrhagic case the kidneys contained 0.213 percent and the serum 0.180. In amyloid nephrosis the kidney contained 0.448 percent, the serum, 0.135 percent. The author concludes that total fat and cholesterol range within normal limits in nephritic kidneys, but possible abnormality is found in the occurrence of much of the cholesterol as esters instead of free. The cholesterol content of the adrenals was about tripled in kidney disease, notwithstanding that the organs were not enlarged. Anemias and infections were attended with low cholesterol in serum and adrenals. Cholesterol was below normal in an amyloid liver, but high in proportion to the diminished total fat.

47.—Beumer, H. Ueber nephrotische Hypercholesterinämie und die Frage ihrer diätetischen Beeinflussbarkeit. *Arch. f. Kinderh.*, 73, 1920, 105, 117. A wide independence of hypercholesterolemia and diet was found, in that lipoid-poor diet did not reduce, and lipoid-rich diet did not increase cholesterol in the post-digestive blood.

48.—Beumer, H. Ueber das Verhalten der Serumlipase unter verchiedenen Bedingungen. *Berl. klin. Woch.*, 58, 1921, 855. No significance of serum lipase has yet been demonstrated in diabetes, tuberculosis, infantile diarrhea and malnutrition, and other clinical disorders investigated.

49.—Bierry, H. Sur le minimum de sucre et le minimum de graisse. *C. r. soc. Biol.*, 82, 1919, 124-127. Theoretical argument favoring the view that a certain minimum of fat as well as of sugar is necessary for health.

50.—Blatherwick, N. R. Observations on blood fat in diabetes. *J. Biol. Chem.*, 49, 1921, 193-199. Blood fat analyses on Newburgh diets show "that cases of mild and moderate diabetes are apparently able to utilize satisfactorily large amounts of fat, as indicated by constancy of the blood fat level and by the absence of acetone bodies in the urine. It remains to be learned whether or not such high fat diets continued for a considerable period will prove to be an overstrain on the fat burning mechanism".

51.—Blau, N. F. and Nicholson, S. T. Fat metabolism in diabetes mellitus, *Arch. Int. Med.*, 26, 1920, 738-750. Studied 34 diabetic cases in Clifton Springs sanitarium. Distinguished 4 groups: 1. blood fat increases steadily or intermittently while sugar comes down:

2. blood fat parallels blood sugar; 3. blood fat remains at practically same level while blood sugar decreases; 4. unclassified, because of insufficient data. Higher blood sugar seems sometimes to favor fat utilization. High fat and cholesterol are reckoned among bad prognostic signs, often associated with nephritis, arteriosclerosis and high blood pressure. Infections sometimes seem to influence blood fat.

52.—Bleibtreu, M. Fettmast und respiratorischer Quotient. *Pflügers Archiv.*, 85, 1901, 345-400. Geese stuffed with rye meal showed milky serum containing as much as 6.126% of ether extractable material. Stuffing with a fat-poor diet of potato, sugar, and egg albumin resulted in clear serum with fat content of 0.35%. Respiratory quotients in stuffed geese were as high as 1.33, indicating fat formation from carbohydrate.

53.—Bloor, W. R. On fat absorption. III. Changes in fat during absorption. *J. Biol. Chem.*, 16, 1913-14, 517-529. On feeding various kinds of fat, the melting point and iodine number of the fat in the chyle are found changed toward those of the animals' body fat.

54.—Bloor, W. R. A method for determination of fat in small amounts of blood. *J. Biol. Chem.*, 17, 1914, 377-84. Description of nephelometric method, and some figures for blood fat of animals.

55.—Bloor, W. R. Studies on blood fat. I. Variations in the fat content of the blood under approximately normal conditions. *J. Biol. Chem.*, 19, 1914, 1-24. After feeding fat the blood fat rose gradually from 0.5 — 0.7% to 1.2 — 1.3%, the maximum being about the sixth hour. Ligation of thoracic duct prevented this lipemia. Fat injected intravenously in emulsified form disappeared rapidly from blood. Dogs having much body fat showed increase of blood fat in fasting. There was found a decided increase of blood fat after etherization, little effect from alcohol, variable results from chloroform, and after morphine no appreciable rise for eight hours, but a considerable rise in the next few days. The nearly constant figure of 0.59% blood fat in normal dogs suggests a delicate regulatory mechanism.

56.—Bloor, W. R. Studies on blood fat. II. Fat absorption and the blood lipoids. *J. Biol. Chem.*, 23, 1915, 217-326. Feeding of the same quantities of fat gives different degrees of lipemia in different animals and in the same animal at different times. Variations in cholesterol are slight or absent. Lecithin is increased 10 to 35 percent in all experiments, roughly parallelling the total fat, but the rise of lecithin often coming later. Consideration is given to Leathes' hypothesis that lecithin is an intermediary in fat metabolism.

57.—Bloor, W. R. The distribution of the lipoids ("fat") in human blood. *J. Biol. Chem.*, 25, 1916, 577-599. Lipoid analyses on 23 normal and 25 abnormal bloods, and a theoretical discussion of fat metabolism.

58.—Bloor, W. R., Joslin, E. P., and Hornor, A. A. The lipoids ("fat")

of the blood in diabetes. *J. Biol. Chem.*, 26, 1916, 417-430. Tables of blood lipoids of 36 treated and 2 untreated diabetics. The percentages in mild cases may be normal, low or high, but in all severe cases the blood fat is twice or more the normal figure. In the heaviest lipemia the total fat was 11.2 percent and the cholesterol 1.5 percent in plasma, while the lecithin values were not greatly increased. In diabetes the corpuscle lipoids remain practically unchanged. The whole picture contrasts with normal alimentary lipemia, in which the total fatty acids are increased in the corpuscles, often to a greater extent than in the plasma. Lecithin is increased only in the corpuscles, and cholesterol is practically unchanged. The blood corpuscle percentage was normal in all but the severest lipemias. There was no definite relation between the degrees of lipemia and acidosis, and even fatal coma may occur without marked change in blood lipoids. Clear diabetic plasma sometimes becomes milky when standing 24 hours, supposedly because some unknown compound is broken up.

59.—Bloor, W. R., and Knudson, A. Cholesterol and cholesterol esters in human blood. *J. Biol. Chem.*, 29, 1917, 7-13. Rather constant relation between cholesterol and its esters in normal blood, variations about 15%. Relation normal in pathological conditions except cancer and most cases of nephritis, in which ester portion was low. Cholesterol esters high in pregnancy. Few if any cholesterol esters in corpuscles. Constancy of relation, even though cholesterol is up to several times normal in diabetes, or down to half normal in pernicious anemia, is interpreted in favor of its importance in fat metabolism.

60.—Bloor, W. R., and MacPherson, D. J. The blood lipoids in anemia. *J. Biol. Chem.*, 31, 1917, 79-95. A study of pernicious, Bothriocephalus and other anemias with reference to the hypothesis of unsaturated fatty acids as etiologic agents. The blood lipoids were found nearly or quite normal, as long as the red cells were above half the normal number. With less than this number of cells, the lipoid changes in order of frequency and magnitude were: (1) high fat in plasma; (2). low cholesterol in plasma and occasionally in corpuscules; (3) low lecithin in plasma. The lipoid composition of the corpuscles was normal on almost all occasions. Splenectomy increased total fatty acid and lecithin in corpuscles and cholesterol in plasma. Though there is no evidence that lipoid abnormalities are a cause of anemia, the low cholesterol (antihemolytic) values and high fat fraction (possibly hemolytic lipoids) are considered suggestive.

61.—Bloor, W. R. The blood lipoids in nephritis. *J. Biol. Chem.*, 31, 1917, 575-583. Analyses in 23 cases of nephritis of various types. "Acute" lipemia like alimentary lipemia, with high fat and lecithin in the plasma and high lecithin in the corpuscles, is distinguished from a "chronic" form, characterized by high cholesterol. The abnormalities in the blood lipoids in severe nephritis were

found to be high fat in plasma and corpuscles and high lecithin in the corpuscles. The cholesterol values were practically normal. These abnormalities are the same as are found in alimentary lipemia and for this reason are regarded as the result of a retarded assimilation of fat in the blood, which in turn is thought to be one manifestation of a general metabolic disturbance brought about by a lowered "alkali reserve" of the blood and tissues.

62.—Bloor, W. R. Lipemia. *J. Biol. Chem.*, 33, 1918, X. Blood lipoid analyses are shown in a diabetic case with over 13 per cent total blood fat, and further figures during about 30 days under treatment. In the first 20 days the diet was practically fat-free and not above 350 calories. In the beginning there was marked "diabetic anemia", the corpuscle percentage being 29 as opposed to normal of 42% for this individual. The lipoid values at first actually increased with concentration of the blood. The total fat became reduced only after subsidence of the acidosis, but the decline of cholesterol was fairly uniform without much relation to the acidosis. An increase of diet to over 1000 calories, including 50 to 60 gms. of fat, only slightly retarded the fall of lipemia.

63.—Bloor, W. R. Methods for the determination of phosphoric acid in small amounts of blood. *J. Biol. Chem.*, 36, 1918, 33-48.

64.—Bloor, W. R. The distribution of phosphoric acid in normal human blood. *J. Biol. Chem.*, 36, 1918, 49-57. Observations and discussion of the possible utilization of lecithin by conversion into neutral fat and discharge of the phosphoric acid.

65.—Bloor, W. R. Blood phosphates in the lipemia produced by acute experimental anemia in rabbits. *J. Biol. Chem.*, 45, 1920, 171-187. Liopid P is most markedly affected by anemia and the consequent lipemia. Values up to five times normal have been found in the plasma, and twice or over the normal value in corpuscles. Any marked rise of lipoid P is attended by increase of inorganic P, but no corresponding change in other forms of P. Inorganic P thus appears to be the form most directly related to lipoid P. Organic P in the corpuscles remains remarkably constant. In the plasma it varies greatly, being sometimes entirely absent, but is generally increased by bleeding.

66.—Bloor, W. R. Lipemia, *J. Biol. Chem.*, 49, 1921, 201-227. Comparison of alimentary, hemorrhagic and diabetic lipemia, from his own figures and those of others. "The characteristics of persistent lipemia as shown by the evidence so far avaliable are as follows: 1. In lipemia of whatever origin, all the blood lipoids (fat, lecithin and cholesterol) are increased, fat generally showing the greatest ultimate increase and cholesterol next 2. There is perceptible in most cases, a sequence in the appearance and disappearance of the three lipoids, fat being the first to increase, lecithin next, and cholesterol last, while during the clearing up of the lipemia the fat diminishes first and the cholesterol last. High values for lecithin and cholesterol often persist for some time after the fat has

reached approximately normal values. 3. In most instances, the values for the ratio lecithin: cholesterol are markedly below normal, due to the greater increase of cholesterol over lecithin. 4. The fat which produces the lipemia may be of endogenous or exogenous origin, or both, but the phenomena of the lipemia are the same in either case. 5. The cause of the lipemia being regarded as a disturbance of the balance between inflow and outflow of fat in the blood, the immediate causative factor in the hemorrhagic lipemia is probably an abnormally large inflow of fat, while in diabetic lipemia it is an abnormally slow outflow".

67.—Bloor, W. R. Fat transport in the animal body. *Physiol. Reviews*, 2, 1922, 92-115. General review and literature.

68.—Boggs, T. R., and Morris, R. S. Experimental lipemia in rabbits. *J. Exp. Med.*, 11, 1909, 553-560. The first description of hemorrhagic lipemia in rabbits. As the lipemia occurred on fat-poor diet, was accompanied by loss of weight, and disappeared when the emaciation became extreme, it evidently originated from the body fat. The opacity of the serum could not always be cleared by the centrifuge or fat solvents. Mention is made of moderate lipemia in a case of human anemia, secondary to hemorrhoids.

69.—Borberg, N. C. Zur Biochemie der Lipoiden. *Skand. Archiv. f.* Physiol., 32, 1915, 287-351. Two types of pathological changes are found in the adrenal cortex: 1. increase of cholesterol compounds in pregnancy and chronic nephritis; 2. diminution of cholesterol and fat in the zona fasciculata and increase of fatty acid, with infiltration of phosphatids from the blood, in most intoxications and infections. The results are taken to suggest an antitoxic process, in which the lipoids play the essential role and the deposit of neutral fat is merely incidental.

70.—Bottazzi, F., and Schifano. Researches on fat metabolism. I. Introduction and scope, II. Existence of a lipase in adipose tissue. Atti. d. R. Accad. Medico-Chirurgica di Napoli, 1916, Part. 1. No lipase was found in the adipose tissue of normal or starved dogs, contrary to Loevenhart (*Amer. J. Physiol.*, 6, 1902, 331) and Bradley (*J. Biol. Chem.*, 13, 1912-12, 404).

71.—Braeuning, H. Weitere Untersuchungen über Verdauungslipämie. *Zent. f. d. ges. Physiol. u. Path. d. Stoffwechs.*, 4, 1909, 18-31. Found no evidence of a ferment in the blood able to dissolve hemoconia, also no leukocytosis after fat feeding or indication that leukocytes take up the hemoconia.

72.—Brissemoret, A. Sur l'action physiologique de la cholestérine. *C. r. soc. Biol.*, 79, 1916, 409-410. Narcosis from 0.23 gm. cholesterol injected intraperitoneally in 420 gm. guinea pig is compared to effect of morphine.

73.—Bullard, H. H. The microscopical demonstration of fats in tissue sections. *J. Med. Research*, 22, 1912-13, 55-65. After analysis of various staining methods, etc., concludes current doctrine that fat is present in invisible and unstainable form in tissues is probably due to faulty technique. "Future investigations may be expected to

show that little or no neutral fat is present in the tissues in such a form that it cannot be microscopically demonstrated in histological preparations".

74. Caro, L. Fettspaltende Fermente im menschlichen Blutserum, ihre Abhängigkeit vom krankhaften, namentlich Kachektischen Zuständen, ihre Unabhängigkeit von der histologischen Zusammensetzung des Blutes. *Ztschr. klin. Med.*, 78, 1913, 286-293. Investigation of lipase in various diseases. Reduction found in cachexia. Lipase was increased in obesity and mild diabetes, normal in a case of severe diabetes. No special changes were found in syphilis or leukemia.

75.—Chalatow, S. S. Ueber das Verhalten der Leber gegenüber den verschiedenen Arten von Spiesefett., *Virchows Arch.*, 207, 1912, 452-469. Refers to Stukkei and Starokadomski. Negative results obtained with sunflower oil, codliver oil and beef tallow fed to rabbits for long periods, while egg-yolk and brain caused deposits of lipoid in cells followed by more or less cirrhosis. Results with rats negative. (Study pertained only to liver).

76.—Chauffard, A. Les dépots locaux de cholestérine et leurs rapports avec la cholestérinémie. *Rev. de méd.*, 31, (2), 1911, 176-194. Analyses show increase of cholesterol in the atheromatous aorta. Hypercholesterolemia found absent with atheroma is assumed to have occurred possibly in the active stage of the lesions. Various conditions of xanthelasma, arcus senilis, retinitis, and cholelithiasis are linked through hypercholesterolemia. A diet including 11 raw eggs daily for three months is supposed to have produced gallstones in a young woman. Low cholesterol diet is advised for all these conditions, and in one case is said to have resulted in absorption of xanthomata.

77.—Chauffard, A., Laroche, G., and Grigaut, A. Le taux de la cholestérinémie au cours des cardiopathies chroniques et des néphrites chroniques. *C. r. soc. Biol.*, 70, 1911, 108-109. Hypercholesterolemia distinguishes nephritic from cardiac patients. It is regarded as an antitoxic reaction.

78.—Chauffard, A. Les variations de la cholestérinémie durant le cycle menstruel. *Presse méd.* 25, 1917, 329-330. Review of work of Gonälons as supporting author's views concerning cholesterol.

79.—Chauffard, A., Laroche, G., and Grigaut, A. Le teneur en cholestérine des surrénales aux différents stades de la vie foetale. *C. r. soc. Biol.*, 81, 1918, 87-89. "As the adrenals increase in size in the fetus the cholesterol content increases until at birth the average amount is 15 gm. per kg. The cholesterol content of the liver and kidney is about 2.5 gm. per kg. at birth". Table shows 0.26% cholesterol at 3 mos. and about 1.5% in new born.

80.—Chauffard, A., Laroche, G., and Grigaut, A. La cholestérinémie a l'état normal et pathologique. *Ann. de Méd.*, 8, 1920, 69-91. All clinical variations of blood cholesterol are related to four general conditions, viz: toxi-infections, nephritis, diabetes, and liver dis-

eases. In the first group, cholesterol is little changed with low grade infections, rises rapidly in severe infections (penumonia) and is subnormal in very bad cases. The metabolic disorders show hypercholesterolemia.

81.—Chauffard, A., Laroche, G. and Grigaut, A. Le cycle de la cholestérine dans l'organisms. *Ann. de méd.*, 8, 1920, 149-172. Cholesterol metabolism is considered to be governed by three factors, viz: diet, internal secretory glands, and liver. Cholesterol analyses are given for various organs of fetus and new-born. In a dog fasting 18 days, serum cholesterol rose from 0.23 to 0.42%, while the organs lost cholesterol in parallel. Changes are shown in nephritis, menstruation, etc. Cholesterol of bile reflects that of the serum.

82.—Chauffard, A., Laroche, G., and Grigaut, A. Les depots locaux de cholestérine; rapports entre la cholestérine circulante et la cholestérine fixée. Ann. de méd., 8, 1920, 321-334. Theoretical discussion and defense.

83.—Connstein, W. Ueber fermentative Fettspaltung. *Ergebnisse d. Physiol.*, 3, 1904, Abt. 1, 194-232. Disappearance of fat is shown when chyle is mixed with blood, by reason of a change to a water soluble, ether insoluble form. The red corpuscles and oxygen are factors.

84.—Cordier, Boulud, and Colrat. L'hypercholestérinémie dans les néphrites chroniques avec hypertension. J. d'urol., 9, 1920, 81-87. High blood cholesterol is found in a few hypertension cases, and is regarded as important for diagnosis, prognosis, and treatment by low cholesterol diet.

85.—Cowie, D. M., and Hoag, L. A. Studies in blood fat. Preliminary report. *J. Amer. Med. Assn.*, 77, 1921, 1493-1494. In thirty determinations on children with non-medical aliments the total blood lipoids averaged 0.7%. The maximum lipemia after ingestion of cream occurred in 5 to 7 hours in children and adults, corroborating Bloor's results on dogs. Diabetic lipemia was reduced with diets high in fat, viz: 100 to 200 gm. fat daily, furnishing adequate caloric intake. A patient having 8.8% blood fat at entrance was discharged with 1.5% (14 hours after a meal). "Starvation produced a 182 percent increase in the total blood lipoids in four days in a 7 year old boy, accompanied by the acidosis picture of diabetes. Another patient showed a 64 percent increase in 3 days of starvation, and this was also accompanied by a marked acidosis. The lipoids of the blood were rapidly decreased when the patients were given a diet high in fat and low in carbohydrate and protein". Some decreases in blood fats were also found during reaction to foreign protein injection.

86.—Craig, C. F. and Williams, W. C. Experimental observations upon the effect of cholesterolemia on the results of the Wassermann test. *Amer. J. Syphilis*, 5, 1921, 392-400. Daily feeding of 1.25 gm. cholesterol per kg. of weight enormously increases the blood

cholesterol of rabbits, but no positive Wassermann test in thus produced. In one instance the serum cholesterol before feeding was 117.6 mg. per 100 cc., on the ninth day 180.2 mg., on the eighteenth day 877.5 mg., and twelve days after discontinuance of cholesterol 961.5 mg.

87.—Cramer, W. On lipoid deposits in adipose tissue. Phys. Proceedings, *J. of Physiol.*, 51, 1917, pp. XI-XII. Adipose tissue contains anisotropic material, apparently a mixture of several lipoids, including cholesterol esters, within the isotropic globules of true fat. The distribution is irregular and the adipose tissue about the kidneys and adrenals is specially rich in lipoids.

88.—Cramer, W. On glandular adipose tissue, and its relation to other endocrine organs and to the vitamine problem. *Brit. J. Exper. Path.*, 1, 1920, 184-196. In all types of mammals yet studied there is a glandular type of fat tissue, histogenetically distinct from ordinary adipose tissue. It is very vascular and rich in cholesterol and other lipoids. On vitamine-free diet, the lipoids disappear from the adrenal cortex and from this fatty tissue, which does not return to flattened connective tissue cells like ordinary adipose tissue, but retains the appearance of a very vascular glandular organ. The name of "lipoid gland" or "cholesterin gland" is suggested.

89.—Cramer, W. Vitamines and lipoid metabolism. *Proc. Physiol. Soc.* (London) 54, 1920-1921, pp. II-IV. In mice and rats on vitamine-free diet the fat disappears from ordinary adipose tissue and the glandular lipoid tissue may become completely free from fat and lipoid globules. After death from vitamine-free diet, the lipoids of the adrenal cortex have almost disappeared. It is suggested that the lipoid glandular tissue plays a part as a store-house of vitamines.

90.—Csonka, F. A. A critique of certain data on the content of cholesterol and fatty substances in the blood, together with a modification of the colorimetric method for estimating cholesterol. *J. Biol. Chem.*, 24, 1916, 431-438. Subnormal blood cholesterol was found in three cases of pernicious anemia.

91.—Csonka, F. A. The fatty acids in human blood in normal and pathological conditions. *J. Biol. Chem.*, 33, 1918, 401-409. Unsaturated fatty acids are a product of normal metabolism and form 48 percent of the total fatty acid of normal blood. The iodine numbers in pathological cases are generally above normal, especially with low hemoglobin values, but as such acids exist in normal blood the cause of anemias must be sought elsewhere.

92.—Csonka, F. A. A study of the nephelometric values of cholesterol and the higher fatty acids. II. *J. Biol. Chem.*, 41, 1920, 243-249. Nephelometric analyses should compare like rather than unlike lipoids.

93.—Cunningham, R. H. Absorption of fat after ligature of the biliary and pancreatic ducts. *J. Physiol.*, 23, 1898, 209-216. Fat absorp-

tion after ligature of both ducts is reduced in rate and quantity, but normal in quality.

94.—Danilewski, B. De l'influence de la lecithine sur l'activité du coeur. *J. d. physiol. et de path. gen.*, 9, 1907, 909-924. Lecithin and cholesterol are found to be powerful heart stimulants.

95.—Danilewski, B. Ueber die Wirkung des Cholesterins auf 's Froschherz. *Pflüger's Arch.*, 120, 1907, 181-192. Cholesterol is found to be a heart stimulant affecting the cardiac muscle directly.

96.—de Langen, C. D. Echanges cholestériniques et pathologie de la race. *Presse Médicale*, 24, 1916, 332-333. (*Abstr. J. Amer. Med. Assn.*, 67, 1916, 841). The blood of natives of the Dutch East Indies contains only about one-half as much cholesterol as that of Europeans, and the cholesterol content of the bile is extremely low. In Japan the figures are said to be about midway between those in the Dutch Indies and in Holland. Gallstones are very rare in the East Indies, and when they occur they are composed of Ca bilirubinate instead of the usual cholesterol. Also among Japanese and East Indians diabetes is said to be rare and the blood pressure low. Granular nephritis is rare. The author does not decide whether low cholesterol is due to diet or race.

97.—Denis, W. Cholesterol in blood under pathological conditions. *J. Biol. Chem.*, 29, 1917, 93-110. Applied Bloor's method to 20 normal and 254 pathological bloods. Normal values occurred at all stages of nephritis, cardiorenal diseases, and arteriosclerosis (but renal cases were on "nephritic" diet poor in cholesterol). No increase was established in pregnancy, syphilis, acute infections, gallstones, even with severe icterus, cirrhosis of liver, malignant diseases, or blood diseases, except for subnormal values in severe primary and secondary anemias. In hyperthyroidism the cholesterol was just below and in one myxedema case just above upper normal limit. Of 25 diabetics, 5 showed slight increase of cholesterol, not related to level of sugar or acetone bodies in blood or urine. It is concluded that cholesterol determinations are of no value in diagnosis or prognosis of disease.

98.—Denis, W. and Minot, A. S. Cholesterol in milk. *J. Biol. Chem.*, 36, 1918, 59-61. Determination in cow's milk by Bloor's method showed direct and proportional variation of cholesterol (17.6 to 10.5 mg. per 100 cc.) with total fat content (5.0 to 3.2%). As samples were all from one dairy the relation may be attributed to constant food supply, as compared with widely varying relations found by the authors in human milk (38 to 9.6 mg. per 100 cc.). As blood cholesterol has relation to diet, this factor probably holds for milk, though experimental proof is lacking.

99.—Dewey, K., Experimental hypercholesterolemia. *Arch. Int. Med.*, 17, 1916, 757-785. Intravenous and intraperitoneal injections of cholesterol emulsions readily produced deposits in organs, interpreted as not merely infiltration but injury of protoplasm. The accumulation in the blood is much less than the quantities de-

posited in the liver, kidneys, and other organs. Parenchymatous degeneration follows, and the urine generally contains appreciable quantities of cholesterol. Hypercholesterolemia may give rise to gallstones in sterile bile, after desquamation of epithelial cells due to irritation by the excess of cholesterol.

100.—Di Stefano, S., The cholesterol content of the blood serum with exudative diathesis. (*Abstr. J. Amer. Med. Assn.*, 70, 1918, 659). The serum cholesterol of infants was found lower than the adult figure, up to 15 months of age. In 12 out of 20 cases of exudative diathesis, the cholesterol was subnormal . It is therefore suggested as a possible etiologic factor.

101.—Dormeyer, C. Die quantitative Bestimmung von Fetten, Seifen und Fettsäuren in thierischen Organen. *Pflügers Arch.*, 65, 1896-7, 90-108. Ether extraction of muscle tissue for months continuously fails to extract the full quantity of fat obtainable after peptic digestion. A combined form of fat is thus proved.

102.—Drummond, J. C. and Halliburton, W. D. Feeding experiments on animals. *J. Physiol.*, 52, 1918, 339-343. Fatty acids in the proportion of 5 to 10 per cent. of the total fat of the diet are found to be harmless.

103.—Dubin, H. Studies of the blood fat and lipoids of the dog before and after the production of experimental anemia, *J. Biol. Chem.*, 33, 1918, 377. By Bloor's methods, the total fats were found slightly increased and lecithin and cholesterol decreased in a dog with trypanosome anemia.

104.—Ellis, G. W., and Gardner, J. A. The origin and destiny of cholesterol in the animal organism. Part IX. *Proc. Roy Soc. London*, B., 85, 1912, 385-393. "A function of the liver is to break down dead cells and eliminate their cholesterol in the bile. After the bile has been passed into the intestine in the process of digestion, the cholesterol is re-absorbed, possibly in the form of esters, along with the bile salts and is carried in the blood stream to the various centers and tissues for reincorporation into the constitution of new cells." The cholesterol content of blood is considered dependent on the sterol content of food. In inanition, both blood and liver contain increased amounts of both free and compound cholesterol, as the animals are living on their own tissues. The cholesterol content and the relation of free and combined forms in muscle, kidney and lung seem independent of diet. Lung has a higher cholesterol content (0.5%) than any other organ except brain (2.02-2.88%). The bile of normal rabbits on green food contained no cholesterol, but after intraperitoneal injection of cholesterol and olive oil, the bile contained 1.226% of free cholesterol and no esters.

105.—Epstein, A. A., and Rothschild, M. A. Concerning the lipoids of the blood in renal conditions, with special reference to the cholesterol content. *Amer. J. Physiol.*, 42, 1917, 586-587. "By a comprehensive study of the chemistry of the blood, effusions and of the urine in renal and other conditions, the conclusion has been

reached that a type of renal affection exists, commonly known as chronic nephrosis, in which the pathological and chemical basis is that of a nutritional disorder." Epstein has formerly emphasized a group of chronic parenchymatous nephritis cases, different from other renal affections and fundamentally a constitutional disturbance. The conclusions is based on changes in protein of blood serum and chemical composition of the effusions. Nearly 100 cases of renal and allied conditions were studied by the new methods for fat and lipoids. Results were summarized as follows: In this type of chronic nephrosis, particularly in the edematous stage, blood lipoids are very high; e.g., cholesterol as high as 1.226 gm. per 100 cc. In other renal conditions, including surgical cases, no such increase has been encountered; occasionally a moderate rise, but as a rule with some superimposed condition. In uremic cases, especially with high blood N, lipoid content is much diminished; cholesterol may fall as low as 0.080 gm. per 100 cc. Several effusion fluids from cases of chronic nephrosis have shown only traces of lipoids, and the urines when rich in protein show small amounts of lipoid. Origin of increased lipoids is not clear; doubtless much of it is from food; some possibly due to mobilization of body fat, particularly as such cases when recuperating show extreme emaciation. "The finding evidently represents a condition of fat non-utilization comparable to that found in diabetes and other nutritional disorders. This is evidenced also by the fact that when a diet consisting of large amounts of protein, a small amount of carbohydrate and practically no fat, is administered for a long period of time, the excessive lipemia and lipoidemia gradually subside."

106.—Epstein, A. A. Further studies on chronic parenchymatous nephritis (chronic nephrosis). *Proc. Amer. Soc. for Clinical Investigation,* 1921, 27-27. Edema of chronic nephrosis is considered extrarenal in origin and due to reduced protein content of blood. Very high protein diet is recommend for treatment.

107.—Erben, F. Zur Kenntniss der chemischen Zusamensetzung lymphämischen Blutes. *Ztsch. klin. Med.,* 40, 1900, 282-293. Serum analyses in two cases of lymphatic leukemia were normal except for low cholesterol and high calcium. In the corpuscles of one case, iron and cholesterol were considerably reduced, and chlorine and lecithin increased. The greatly increased number of leukocytes is suggested as the explanation.

108.—Erben, F. Ueber den Lezithingehalt der Erythrocyten bei Diabetes mellitus. *Ztsch. f. inn. Med.* 28, 1907, 1090-3. Lecithin and cholesterol were found reduced in the red corpuscles of diabetic blood, while the content of the plasma was little altered. The possibility is suggested that the defective composition may extend to all body cells.

109.—Escher, H. H. Grundlagen einer exacten Histochemie der Fettstoffe. *Cor. Bl. f. schweiz. Aertzte,* 49, 1919, 1609-1623. Considerable review of literature, and colored plate showing staining reactions

of different fatty compounds. Author thinks stains should be applied for study of physiological reactions.

110.—Evans, H. M. The macrophages of mammals. *Amer. J. Physiol.*, 37, 1915, 243-258. Macrophages which are endothelial in nature line the following: Capillaries of the hepatic lobules, capillaries and venules of the spleen, bone-marrow and hemal glands, lymphatic sinuses of the lymphatic glands. Other macrophages which are more or less fixed cells include, first, cells endothelial in appearance and probable origin, but not in vascular channels; chief among these are reticulum cells of lymph glands and similar cells in splenic pulp and bone marrow. Second, cells not directly related to endothelium, chiefly clasmatocytes or resting wandering cells of connective tissue. Rather rounded free strains of these cells occur in the omentum, where they form the colonies known as taches laiteuse. The free macrophages comprise the characteristic mononuclear cells of the serous cavities, similar mononuclear cells often abundant and always present in lymphatic sinuses of lymph glands, and similar cells sometimes present in splenic and hepatic capillaries and under rarer conditions in the peripheral blood stream.

111.—Fahr, Zur Frage des diabetischen Xanthoma. *Dtsch. med. Woch.*, 45, 1919, 1913. Description of unique case in which xanthomata consisted chiefly of infiltration of neutral fat. Very few "xanthoma cells" loaded with cholesterol were present. The capillaries in the kidneys and other organs were distended with stainable fat, indicating heavy lipemia.

112.—Faust, E. S. Ueber chronische Olsäurevergiftung. *Arch. exp. Path. and Pharm.*, 59 Suppl., 1908, 171-175. In continuation of the Bothriocephalus anemia studies of the author and Tallqvist, oleic acid was given to dogs subcutaneously and by mouth. Chronic poisoning with the acid was found to produce marked anemia.

113.—Feigl, J. Neue Untersuchungen über akute gelbe Leberatrophie. III. Fette und Lipoide des Blutes. *Biochem. Ztschr.*, 86, 1918, 1-47. In the later stages of acute yellow atrophy, the total fatty acids may reach 1023 mg. per 100 cc. of plasma, neutral fat 400 mg., free fatty acids 200 mg., and total cholesterol 960 mg. Ratio of total fatty acids to lecithin may be about 10, while ratio of lecithin to cholesterol may drop to 0.1.

114.—Feigl, J. Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden im Blute bei Geisteskraheiten. (Neue Beobachtungen zur Kritik der Bornstein-Peritzschen Lecithinämie.) *Biochem. Ztschr.*, 88, 1918, 53-84. Various figures obtained by Bloor's method, of interest chiefly for establishing normal values. Abnormalities of blood lipoids in nervous diseases are found to be inconstant.

115.—Feigl, J. Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden im menschlichen Blutplasma bei Icterus und Cholämie., *Biochem Ztschr.*, 90, 1918, 1-38. In obstructive (including catarrhal) jaundice are found lipemic pictures in which cholesterol is prominent; neutral fat is less prominent and disappears

soon. Lecithin is low, unless with complications. In cases of neoplasm, these results may be modified by cachexia and inanition. Other modifications are introduced by fever, hydremia, fasting, obesity, alcoholism, lues, tabes, and cirrhosis of the liver. Lipemia as high as 3% is sometimes completely masked so that the plasma is clear.

116.—Feigl, J. Neue Beiträge zur Kenntniss des physiologischen Lecithinämie. *Biochem. Ztschr.*, 90, 1918, 361-382. Physiological lecithinemia varies with alimentary condition. With abundant diet it may be as high as 300 mg. and average 250-270 mg. per 100 cc. Its percentage is more constant than that of fatty acids, neutral fat or cholesterol. Differences between the sexes are denied.

117.—Feigl, J. Neue Untersuchungen zur Chemie des Blutes bei akuter Alkoholintoxikation und bei chronischem Alkoholismus mit besonderer Berücksichtigung der Fette und Lipoide. Chemische Untersuchungen zur Kenntnis der Entwicklug und des Aufbaues von Lipämien. V. *Biochem Ztschr.*, 92, 1918, 282-317. Lipemia is found rather frequent with chronic alcoholim. The lipoid increase is almost entirely in the plasma, though some variation may be found in the cells. Correlation of the quantities of circulating fat with the fattiness of organs was not found regular.

118.—Feigl, J. Ueber das Vorkommen von Phosphaten im menschlichen Blute. X. Die nephelometrie der Phosphorsäure als Grundlage der P. Verteilung, speziell der Lecithinämie, im Analysengange von der Grössenordung des Gangschen Systems. *Biochem. Ztschr.*, 102, 1920, 131-140. Chiefly comparisons and interpretations of Bloor and Bang methods.

Feigl, J. Ueber Choleterinämie. I. Vergleichende Untersuchungen zur Methodik mit besonderer Berücksichtigung der colorimetrischen Verfahren. *Ztschr. f. d. ges. exper. Med.*, 11, 1920, 178-238. An intensive review, comparison and criticism of methods.

119.—Feigl, J. Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden im Blute nach Blutentziehung. Chemische Beiträge zur Kenntnis des Lipämiegebietes. VII. *Biochem. Ztschr.*, 115, 1921, 63-70. Chiefly a confirmation of anemic lipemia in rabbits, with Bloor's methods. Lipemia also occurs in some human cases after excessive menstruation or hemorrhage from a gastric ulcer or tuberculous lung. The therapeutic removal of 200 to 500 cc. of blood in nephritis cases may produce lipemia within a few days. When the cholesterol is already high, there may be merely an addition of neutral fat.

120.—Fenger, F. Phosphatids in the ductless glands. *J. Biol. Chem.* 27, 1916, 303-307. Compared with lean meat, the anterior lobe of the pituitary contains ten times, the posterior lobe seven times, the pineal thirteen times, the corpus luteum of pregnancy fifteen times, and the adrenals seventeen times the quantity of phosphatids. The phosphatids are therefore believed to play a part in the internal chemistry of these glands. They are probably not

concerned in the function of the thyroid, which contains no more than muscle.

121.—Fex, J. Chemische und morphologische Studien über das Cholesterin und die Cholesterinester in normalen und pathologisch veränderten Organen. *Biochem Ztschr.*, 104, 1920, 82-174. The free and combined cholesterol of the liver showed very slight variations in the entire series, including two cases of cirrhosis. The kidneys of both normal, and pathological individuals varied widely in free cholesterol, but their combined cholesterol varied little except for an increase in kidney disease. The adrenals were fairly constant in free, but variable in combined cholesterol content. In chronic kidney diseases cholesterol esters are demonstrable morphologically, and the appearances correspond fairly closely with chemical analyses, but this is untrue in other conditions.

122.—Fichtner, R. Zur pathologischen Anatomie der Nieren beim Diabetes mellitus. *Virchows Arch.* 114, 1888, 400-406. In certain diabetic kidneys, in addition to the glycogenic degeneration of Henle's tubes, there is another fully characteristic change, viz: a fattiness of the greater part of the renal cortex.

123.—Fischer, B. Ueber Lipämie und Cholesterämie, sowie über Veränderungen des Pankreas und der Leber bei Diabetes mellitus. *Virchows Archiv.*, 172, 1903, 30-71, 218-261. Report of a case of lipemia with 18.129% fat and at least 0.478% cholesterol in the blood. Lipolytic power was supposed to be lacking, for the fat did not diminish in blood samples on standing, but diminished on addition of normal blood.

124.—Forbes, E. B., and Keith, H. M. Phosphorus compounds in animal metabolism. *Ohio Agricultural Experiment Station,* Technical Series, Bulletin No. 5, 1914. A classical review and bibliography.

125.—Franchini, G. Ueber den Ansatz von Lecithin und sein Verhalten im Organismus. *Biochem Ztschr.*, 6, 1907, 219-225. Lecithin feeding of rabbits increases lecithin content of liver and muscles but not of brain. The increase in the liver may persist as long as fifteen days after discontinuance of the dosage.

126.—Fraser, Mary T., and Gardner, J. A. The origin and destiny of cholesterol in the animal organism. Part VII. On the quantity of cholesterol and cholesterol esters in the blood of rabbits fed on diets containing varied amounts of cholesterol. *Proc. Roy. Soc. London. B.* 82, 1909-1910, 559-568. The free and combined cholesterol of rabbits' blood varied with the sterols of the diet. The antihemolytic power of the blood increased with high cholesterol.

127.—Frugoni, C., and Marchetti, G. Beitrag zum Studium der diabetischen Lipoidämie. *Berl. klin. Woch.*, 45, 1908, 1844-1846. Clinical, chemical and pathological studies of one diabetic case and suggestion of the name lipoidemia because of the high proportion of lipoids. The blood of this thirteen year old boy con-

tained 27% ether extract, 1.063% cholesterol and 0.511% lecithin. After death in coma three days later the autopsy blood contained 24% ether extract, 1.41% cholesterol and 0.644% lecithin. The urine contained 0.0875% fat, or 3.5 gm. in 24 hours.

128.—Gade, H. E. Contribution to the knowledge of resorption of fats; the quantitative method for the determination of these and of alimentary lipemia. *Bibliot. f. Laeger,* Copenhagen, 111, 1919, 1-160. (Original not available).

129.—Gamble, J. L., and Blackfan, K. D. Evidence indicating a synthesis of cholesterol by infants. *J. Biol. Chem.,* 42, 1920, 401-409. In tests on 4 thriving infants for three days, the feces contained 1.7 to 3.4 times as much cholesterol as the diet, indicating a synthesis of cholesterol in the body.

130.—Gardner, J. A. and Lander, P. E. On the cholesterol content of the tissues of cats under various dietetic conditions and during inanition. *Biochem. J.,* 7, 1913, 576-587. The cholesterol of broken down cells is partly used for formation of new cells and partly excreted by the liver in the bile. This cholesterol is partly resorbed in the intestine, and deficits are supplied from the food.

131.—Gaudissart, P. Hypercholesterinemia and albuminuric retinitis. *Amer. J. of Ophthalmology,* 5, 1922, 118-122. Study of a series of cases indicated no relation between hypercholesterolemia and the exudate of albuminuric retinitis.

132.—Geelmuyden, H. C. *Norsk. Mag. f. Laegevidenskaben,* 81, 1920, 479-492; 578-594. Am fettvandring. (Same as 133).

133.—Geelmuyden, H. C. Ueber Fettwanderung. *Acta Med. Scandinav,* 54, 1920-21, 51-64; 147-163. The author believes in the formation of sugar from fat in the liver, and thinks that ketone bodies disappear not through combustion but through transformation into sugar in the liver. The syndrome of ketonuria, absence of glycogen, and fatty liver is found in a series of clinical and experimental conditions, with or without glycosuria. In the glycosuric group are diabetes and phlorizin poisoning, in the non-glycosuric group poisoning with phosphorus, chloroform, etc. Some of the differences between human diabetics and totally depancreatized dogs are found in the lipemia and fatty liver. The experimental chronic diabetes of Sandmeyer and Langfeldt more closely resembles the clinical form.

134.—Goñalons, G. P. Variaciones de la colesterinemia durante el ciclo menstrual. *Semana méd.,* 23 (2), 1916, 639-642. Describes menstrual cycle of blood cholesterol. On some day, five to seven days before menstruation, there is a sharp rise to 0.200 - 0.324 percent. Several fluctuations occur thereafter, and a fall to 0.150 — 0.175 percent after cessation of the flow. The specific character of the phenomenon is substantiated by atypical findings in sexual disorders.

135.—Goñalons, G. P. Litiasis biliar e hipercolesterinemia menstrual. *Revista Assoc. med.* Argent. 26, 1917, 1091-1093. Similar to (134).

136.—Gorham, F. D., and Myers, V. C. Remarks on the cholesterol

content of human blood. *Arch. Int. Med.*, 20, 1917, 599-612. Determinations in about 200 patients with 25 diseases showed hypercholesterolemia usually though not invariably in arteriosclerosis, nephritis, obstructive jaundice and diabetes; and hypocholesterolemia in cachexia of malignancy and in all anemias of pernicious type. The inconstancy of hypercholesterolemia with cholelithiasis impairs its diagnostic value.

137.—Gratia, A., and Levene, P. A. The role of cephalin in blood coagulation. *J. Biol. Chem.*, 50, 1922, 455-461. Testing the views of Bordet, Howell and others with purer material than previously available, the authors find that lecithin has practically no influence upon coagulation, while cephalin is highly active.

138.—Gray, H. Lipoids in 131 diabetic bloods. *Boston Med. and Surg. Jour.*, 178, 1918, 16-20, 50-55, 91-94. Numerous detailed observations impossible to summarize. Patients much under normal weight (i.e., severe type) showed rise in all blood lipoids; those over weight averaged slightly above normal in total fatty acids and glycerides of plasma and slightly below normal in glycerides of corpuscles, in lecithin and cholesterol. Therapeutic reduction of weight lowered the total blood fat. In diabetic lipemia the increase of fatty substances is greater in the plasma than in the corpuscles. The increase consists chiefly in neutral fat, next in cholesterol, and least in lecithin. High cholesterol is characteristic of chronic as opposed to acute (e. g. alimentary) lipemia. The blood lipoids were generally lower in the cases of longest standing, supposedly because of their emaciation. On fasting they may rise at first, but become lower at the third day. Acidosis and lipemia are found together but not parallel; the increase of lipoids was found twice as great with moderate as with severe acidosis. Etherization in one case was followed by a slight transitory lipoid increase. There were no differences between the sexes. The higest lipemia observed was 16.34%.

139.—Greene, C. W. and Summers, W. S. The fat and lipase content in the blood in relation to fat feeding and fasting. *Proc. Am. Phys. Soc.*, Dec. 1915. *Am. Jour. Physiol.*, 40, 1916, 146-147. Alimentary lipemia is accompanied by rise of lipase. Variations in fasting are described.

140.—Grigaut, A. and l'Huillier, A., Taux comparé de la cholestérine des hematies et du sérum dans le sang normal et pathologique. Variations in cholesterolemia occur only in the serum, and neither in health nor in the various diseases (including one case of diabetes) is the corpuscle content affected.

141.—Grigaut, A., and l'Huillier, A., Hypercholestérinémie d'origine alimentaire chez le chien. Cholesterol increases in the blood but not in the feces after meals containing 1 or 2 gm. cholesterol.

142.—Gröhndahl. *Am Fettemboli*, Kristiania, 1911. (Ref. by Hedrén, p. 936). Thinks question of embolism in diabetic lipemia undecided, and states that pictures resembling true fat embolism are often encountered microscopically in lipemia.

143.—Grubb, A. B. Dropsy in children due to fat starvation. *Virginia Med. Monthly*, 46, 1919, 166. A child of fourteen months after sixty days on a diet of Imperial Granum, following rib resection for lung abscess, developed edema which resisted digitalis and other drugs, and ended fatally. A two year old child placed on nearly fat-free diet for stomach trouble developed dropsy in two months, which cleared up completely on high fat diet.

144.—Gumprecht. Ueber Lipämie. *Dtsch. med. Woch.*, 20, 1894, 756-757. Description of a case of lipemia in a twenty-one year old brewery laborer who had long consumed 5 to 6 liters of beer daily.

145.—Halliburton, W. D. The rôle of fats in diet. *Arch. neerl. de physiol.*, 2, 1917-18, 602-608. Discussion of fats and vitamines, especially in relation to war diet. No experiments described.

146.—Hammarsten, O. Zur Chemie der Galle. *Ergebn. d. Physiol.*, 4, 1905, 1. Abt., 1-22. The analyses show, among other things, that the polar bear with its high fat diet ranks highest among mammals in the lecithin content of the bile, while man holds the second place in this respect. A rôle of lecithin in fat digestion is suggested.

147.—Hanes, F. M. The pathology of fat metabolism. *Bull. Johns Hopkins Hosp.*, 23, 1912, 77-82. A study of fat infiltration of organs.

148.—Hatai, Shinkishi. The effect of lecithin on the growth of the white rat. *Amer. J. Anat.*, 10, 19003-4, 57-66, Young white rats, fed or injected subcutaneously with lecithin, showed 60% greater gain in weight than controls, with correspondingly greater weight of the nervous system and higher resistance to unfavorable surroundings.

149.—Hedrén, G. Fettemboli och diabetisk lipämi. *Svenska Läkaresällskapets Handlinger*, Band 42, H. 3, 1916, 933-946. Literature of fat embolism hypothesis and report of 50 diabetic autopsies. Of these, lipemia as judged by "cream" after centrifuging was slight in 57 and heavy in 3 cases. In 2 of the latter, no emboli were found, but in the third, numerous genuine fat emboli were supposedly demonstrable.

150.—Helly, K. Fettghalt und Fettphanerose in der Leber. *Verh. d. dtsch. path. Gesellsch*, 17, 1914, 136-138. Experiments showed discrepancies between visible fatty appearances in the liver and the content revealed by chemical analyses. Better agreement was found if the sections were first treated with pepsin HCl to show dissolved fat.

151.—Henes, E. Jr. The prognostic value of cholesterinemia in chronic nephritis. *Arch. Int. Med.*, 25, 1920, 411-419. A previous publication reported hypercholesterolemia in cases of nephritis progressing favorably. The present study indicates fall in cholesterol as a bad prognostic sign. In case 12, blood cholesterol fell gradually in six weeks from 797 to 249 mg. per 100 cc., while nonprotein N steadily increased. A protective action of lipoids against toxins is suggested.

152.—Henning, B. H. The lipoids of the blood in tuberculosis. *J. Biol. Chem.*, 53, 1922, 167-170. Concludes that "1. Cholesterol

was found to be uniformly low in tuberculous blood when determined by the saponification method, but normal when determined without saponification. The presence in the blood plasma in tuberculosis of a relatively large amount of an unknown substance which is probably closely related to cholesterol is thus indicated. 2. Total fatty acid and lecithin were within the normal range of values for these substances. 3. The "residual" fatty acid of the blood was high, and since there was no lipemia, the presence of other forms of fatty acid combination than those ordinarily present is suggested".

153.—Henriques, V., and Hansen, C. Ueber den Uebergang des Nahrungsfettes in das Hühnerei und über die Fettsäure des Lecithins. *Skand. Arch. f. Physiol.*, 14, 1903, 390-397. Changes in food fat altered the iodine number of the fat but not of the lecithin in hens' eggs.

154.—Hill, Elsie, and Bloor, W. R. Fat Excretion. *J. Biol. Chem.*, 53, 1922, 177-178. Literature of fecal fat excretion during fasting and on fat-free diets, also of lipoid accumulation in isolated intestinal loops. Fairly constant composition of fatty acids, cholesterol and neutral fat characterizes feces. Authors report one experiment in which a Thiry fistula of 14 inches of jejenum in a 5-day period yielded 0.72 gm. of lipoid material, the dog being well fed during this time. Cats were placed on diets of meat, casein, olive oil, cocoa fat, etc. In summarizing the authors conclude: "When moderate amounts of fat are fed, the fat of the feces is largely independent of the diet, and in composition approaches that from a fat-free diet. The comparative constancy of composition of the feces fat favors the idea of a fat excretion from the intestine, but while an excretion is probable it cannot be regarded as proven, in view of the undetermined influence of lipoid from free cellular material. The feces fat cannot ordinarily be regarded as unabsorbed food fat and, therefore, feeding experiments as a test of the extent of utilization of food fat are of doubtful value unless account be taken of the amount and kind of fat which appears in the feces independently of the food".

155.—Hindhede, M. Fettminimum. *Skand. Arch. f. Physiol.*, 39, 1920, 78-131. Experiments on Frederik and Holger Madsen and others. It is shown that young strong persons can maintain health at least sixteen months on a diet of bread, potatoes, cabbage, rhubarb and apple, without fat addition. Conclusions are drawn regarding fat requirements and war diets.

156.—Hirschberg, E., and Winterstein, H. Ueber den Umsatz von Fettsubstanzen in den nervösen Zentralorganen. *Ztschr. f. physiol. Chem.*, 105, 1919, 1-30. A consumption of fat, apparently by oxidation, is shown to result from stimulation of the isolated spinal cord of frogs, and is preventable by sugar.

157.—Horiuchi, Y. Studies on Blood Fat. 1. Variation of the blood fat constituents of rabbits under normal conditions. *J. Biol. Chem.*, 44, 1920, 345-361. Comparison of blood fat of rabbits

fed respectively on carrots and on sunflower seed showed total fatty acids of blood considerably greater in the latter and almost no difference in lecithin and cholesterol. In rabbit blood, fatty substances in plasma are much less than in corpuscles. Cholesterol is about one third and lecithin one-half that of human plasma, while the lipoid content of the corpuscles approximates the human. The blood fats of an individual animal are practically stable, even with daily bleedings of 10 cc. for three or four days. Further bleedings begin to cause lipemia.

158.—Horiuchi, Y. Studies on blood fat. II. Lipemia in acute anemia. *J. Biol. Chem.*, 44, 1920, 363-379. One bleeding of 45 cc. produced marked lipemia in a rabbit fed on sunflower seed but was less effective on carrot diet. Lipemia from acute anemia begins with slightly cloudy plasma within 24 hours, increases to milky appearance within 48 hours, and reaches heaviest creamy state within 72 hours. This time relation is the same on low as on high fat diets, but the degree is less. After the plasma has become clear, abnormally high fat analyses continue for 14 to 18 days. The increase of lecithin and cholesterol bears no fixed parallelism to total fat. The ratio of total fatty acids to lecithin rises abnormally, but the ratio of total fatty acids to cholesterol is not greatly changed. The lipoid increase occurs only in the plasma and not in the corpuscles. The absence of increase of lecithin in the corpuscles indicates that their lecithin function is deranged in hemorrhagic as well as in diabetic lipemia.

159.—Hueck, W. Die Bedeutung der Nebennieren für den Kohlehydrat und Cholesterinstoffwechsel und über die Beziehungen des Cholesterins zum Fettstoffwechsel. *Verh. d. dtsch. path. Gesellsch.*, 17, 1914, 149-156. Rabbits ordinarily die within a few days after double epinephrectomy. Exceptions indicate the presence of accessory adrenals. Blood sugar falls, as in other species, while cholesterol rises markedly. The adrenals therefore do not form cholesterol, but probably store it from the blood. Removal of the interrenal organs of fish caused death within 24 days without changes in lipoids of blood, liver or muscles. In the autopsy of a case of Addison's disease, the adrenal apparatus was fully normal in appearance and chrome staining and the one abnormality was a complete absence of cortical lipoid. The author believes that fatal adrenal deficiency consists in loss of synergism of medulla and cortex; also that cholesterol furnishes an important means of fat transportation.

160.—Hueck, W. and Wacker, L. Ueber die Beziehungen des Cholesterins zum intermediären Fettstoffwechsel. *Biochem. Ztschr.*, 100, 1919, 84-99. References to former work show that cholesterol feeding increases not only cholesterol but also other lipoids, especially phosphatids in the blood; also that the cholesterol content of human fat is 0.127%, and may be multipled by two or three times in old age or pathological conditions. Figures are given for the blood cholesterol of several species. Esters amount

to two to four times the free cholesterol in serum, but are absent from the corpuscles. These esters are supposedly formed and decomposed by exchanges between cholesterol and glycerol. Cholesterol is regarded as an important intermediary in fat metabolism.

161.—Hutchison, H. S. Fat metabolism in health and disease with special reference to infancy and childhood. *Quart. J. Med.*, 13, 1920, 277-292. Fat digestion in infantile atrophy, rickets and tetany is as efficient as in healthy children. "The fairly constant percentage of fat in the feces of man and other animals suggests that fecal fat has a function to perform and that it is not a pure excretion. There is no evidence, however, to indicate what this function is."

162.—Hymanson, A., and Kahn, M. Lipoid content of maternal and fetal blood. *Amer. J. Obstetrics*, 73, 1916, 1041-1046. Infant blood is generally higher in total lipoids than maternal blood, but sometimes vice-versa. Cholesterol is generally higher in maternal blood. The differences are mostly in the third decimal place, but are considered sufficient for the conclusion that the placenta is impermeable to cholesterol.

163.—Ignatowski, A. Ueber die Wirkung des tierischen Eiweisses auf die Aorta und die parenchymatösen Organe des Kaninchen. *Virchows Arch.*, 198, 1909, 248-270. Animal food (raw meat and egg yolk) was found to cause pathological changes in rabbits, such as anemia, cirrhosis of liver, parenchymatous nephritis, atheroma of aorta and marked hypertrophy of adrenals.

164.—Imrie, C. G. On the fat in the blood in a case of lipemia. *J. Biol. Chem.*, 20, 1915, 87-90. Autopsy report of a diabetic patient with coma and lipemia. The blood serum yielded 14.06% petroleum ether extract and 1.5% cholesterol, practically all in free form. Very little lecithin was present. The blood fats were almost entirely simple glycerides, of iodin value 73, corresponding to 68 in adipose tissue, but differeing widely from those of liver, heart, and kidney (104-132). The total amount of fat in the blood was estimated at 300 gm. or more. It was supposed to come from mobilization of body fat.

165.—Iscovesco, H. *Les lipoides du sang.* Preparation des lipoides des stroma globulaires. *C. r. soc. Biol.* 72, 1912, 920-922. Blood cholesterol follows a diurnal curve, with maxima falling six to eight hours after the two or three meals of the day.

166.—Jansen, B. C. P. Ueber den Fettstoffwechsel beim Fehlen des Pankreassekrets im Darmrohr. *Ztschr. physiol. Chem.*, 72, 1911, 158-66. A dog with a subcutaneous pancreatic graft could utilize up to about 80 per cent of the fat fed. Removal of the graft resulted in a gradual but marked impairment of utilization.

167.—Jarisch, A. Beitrag zur Pharmakologie der Lipoide. I. Versuche an roten Blutkörperchen. *Arch. f. d. ges. Physiol.*, 186, 1921, 299-317. Red corpuscles treated with emulsions prepared from alcohol-

ether organ extracts show increased resistance to hypotonic salt solution, but diminished resistance to various other hemolytic agents. The former effect of lipoids is attributed to their property of making objects less liable to wetting by water.

168.—Jastrowitz, H. Ueber Lipoidverfettung. *Ztschr. exp. Path. u. Ther.*, 15, 1914, 116-166. The author considers quantitative fat infiltration less important than qualitative changes in fat and lipoid composition. In some forms of poisoning, (P., Ol. Pulegii) no such qualitative changes were found; in others (nitro-benzol, vibrio Nasyk) cholesterol was increased. Under certain unknown conditions, liver phosphatids are diminished. Some minor, but not major fatty changes give discrepancies between microscopic and clinical pictures.

169.—Jastrowitz, H. Zur Pathochemie der Blutlipoide bei experimenteller Anämie. *Ztschr. f. d. ges. exper. Medizin*, 27, 1922, 276-304. Various changes in blood lipoids were observed by Bang's method in poisoning with pyrogallol, pyrodine, nitrobenzol, etc. In general the anemias were attended only with minor changes in the individual lipoids, and not with heavy lipemia such as found after hemorrhage. In the chronic poisonings, lipoids diminish in both plasma and corpuscles. Lipoidemia bears no relation to fat phanerosis of parenchymatous organs.

170.—Javal, Amado and Boyet. Lipemia dans un case de diabète maigre. *C. r. soc. Biol.* 70, 1911, 163-165. Report of a case of lipemia with the usual accompaniment of increased lecithin and choleterol in the blood, but no marked deviation from ordinary fat content of organs.

171.—Kalabonkoff, Mlle. L., and Terroine, E. F. *C. r. soc. Biol.*, 63, 1907, 372-374, 617-619, 664-666. Lecithin failed to effect any activation of ferments of pancreatic juice or of gastric or intestinal mucosa.

172.—Kanders, F. Ueber den Cholesterin und Cholesterinestergehalt des Blutes verscheidener Tiere. Cholesterol esters were found absent from dog, rabbit, and guinea-pig corpuscles, 0.019% in beef corpuscles, 0.689% in sheep corpuscles.

173.—Kawamura, R. Die Cholesterinesterverfettung. *Jena*, 1911.

174.—Kawamura, R. Die Cholesterinesterverfettung (Cholesterinsteatose) der Kupfferschen Sternzellen. *Virchows Arch.*, 207, 1912, 469-476. This author's writings give a full exposition of the views of the Aschoff school. Fatty degeneration is divided into three forms according to the predominance of neutral fats, cholesterol esters, and other lipoids. A case is described in which the Kupffer cells of the liver were crammed with anisotropic cholesterol esters, in contrast with the ordinary refusal of these cells to take up cholesterol. In diabetes the fat in the cells is never anisotropic. Staining reactions indicated that it was in one case cholesterol-glycerol esters, in another case, glycerol esters alone. The fat droplets in the diabetic kidney reacted as glycerol esters.

175.—Kawamura, R., and Nekanoin, T. Cholesterinresorption und

Cholesteatose des Darmes. *Verhandl. der Japanischen pathol. Gesellschaft,* 6, 1916, 93-97. Young rabbits were killed at various hours following the feeding of 5 gm. cholesterol in olive oil. The cholesterol was traced microscopically from tips of villi into deeper layers of bowel in the form of esters. Experiments with vital staining after feeding egg yolk or olive oil indicated that considerable quantities of lipoids were deposited in the wall of the intestine itself.

176.—Kipp, H. A. The effect of whole blood transfusion on the cholesterol content of human serum in pernicious anemia. *J. Biol. Chem.*, 43, 1920, 413-420. Cholesterol content of serum declines with severity of anemia, suggesting its use against unknown hemolytic substances. Repeated whole blood transfusion does not greatly raise the serum cholesterol of the patient.

177.—Kipp, H. A. Variation in the cholesterol content of the serum in pneumonia. *J. Biol. Chem.* 44, 1920, 215-237. Variations of serum cholesterol depend upon the extent and severity of the infection. Leukocytes are supposed to transport cholesterol to the inflamed area, where it neutralizes toxins and perhaps aids in developing antigens.

178.—Kipp, H. A. Variations in the total cholesterol content of the blood serum in pernicious anemia and pneumonia. *Proc. Soc. Exp. Biol. and Med.*, 18, 1920-21, 26-27. Serum cholesterol is reduced in pernicious anemia, possibly because it is a protective agent used up in combating the poisons of this disease. For a similar reason cholesterol falls at the outset of severe pneumonia and rises even above normal with convalescence. It falls with empyema and remains low to the time of spontaneous or operative cure. The cholesterol of empyema exudates is found chiefly in the cells.

179.—Kirsche, A. Beiträge zur Frage der lipoiden Organhämolysine und ihrer Beeinflussung durch Traubenzuckerfütterung. *Biochem. Ztschr.*, 55, 1913, 169-188. In experiments with phlorizin, toluylendiamin and other poisonings, the attempt was made to distinguish between fatty degeneration and infiltration of organs on the basis that the lipoids in the former process are more strongly hemolytic than the neutral fat which predominates in the latter process.

180.—Klein, W., and Dinkin, L. *Ztschr. physiol. Chem.*, 92, 1914, 302-330. Analyses of many normal and pathological sera gave few striking results except increased cholesterol in a large majority of the syphilitics.

181.—Klemperer, G., and Umber, H. Zur Kenntnis der diabetischen Lipämie. *Ztschr. klin. Med.*, 61, 1907, 145-52. Diabetic lipemia is characterized as a lipoidemia on the ground of the increase of lecithin and cholesterol, which may make up half or more of the fatty substances in the blood.

182.—Klemperer G., and Umber, H. Zur Kenntnis der diabetischen Lipämie. II. *Ztschr. klin. Med.*, 65, 1908, 340-51. As the excess of

circulating lipoid is not derived from the brain or kidneys, the authors believe that it must come from cell destruction.

183.—Klemperer, G. Ueber diabetischen Lipämie. *Dtsch. med. Woch.*, 36, 1910, 2373-2377. The author adopts the hypothesis that the increase of lecithin and cholesterol in the blood is an expression of increased cell destruction and construction in diabetes.

184.—Klemperer, G. Discussion of papers of Reicher on lipemia and of Funk on renal glycosuria. *Verh. d. dtsch. Kong. f. inn. Med.*, 30, 1913, 175-176. Marked lipemia is characterized as a very bad prognostic sign, generally pointing to early coma.

185.—Klinkert, D. Untersuchungen und Gedanken über den Cholesterinstoffwechsel. *Berl. klin. Woch.*, 50, 1913, 820-825. Cholesterol ester accumulations are abnormal in all organs except the adrenal cortex and the corpus luteum. They are properly a secretion of the adrenal cortex, and its increased content in cholelithiasis, diabetes, nephritis, arteriosclerosis and obesity possibly represents an over-function. These disorders are linked through hypercholesterolemia, xanthelasma, retinitis, etc.

186.—Klotz, O. Vascular changes following intravenous injections of fat and cholesterin. *J. Med. Research.*, 28, 1915-1916, 157-170. Rabbits were injected intravenously with cholesterol in olive oil. Doses of 0.5 to 2 cc. of a one in fifteen solution caused pulmonary embolisms but no apparent harm. Cottonseed oil proved toxic. Sodium oleate lost its hemolytic effect when injected with cholesterol. The pathologic effects of oil injected with and without cholesterol were compared. Cells phagocyting oil and cholesterol seem to separate them; the oil is decomposed by intra-cellular lipolysis, while cholesterol remains as inert material and gives rise to giant cells. Other interesting histologic details are described.

187.—Knack, A. V. Ueber Cholesterinsklerose. *Arch. path. Anat.*, 220, 1915, 35-52. Increase of lipoids in adrenal cortex is found not only with vascular atheroma but also in other diseases, especially infections. Feeding rabbits 0.5 to 4.5 gm. cholesterol per day in bread dough produced no vascular lesions except in two instances in which there was infection. The author believes that not cholesterol as such, but a one-sided abnormal diet (milk, eggs) causes the atheroma reported by other authors.

188.—Knack, A. V., and Neumann, J. Beiträge zur Oedemfrage. *Dtsch. med. Woch.*, 43, 1917, 901-906. In war edema due to faulty diet, water content of serum was found increased about 10%. The blood lipoids behaved as authors have previously found in edema from chronic dysentery. Reference is made to Feigl's findings of reduction of all lipoids in the plasma, also of the lecithin of the red corpuscles, while the cholesterol content of the corpuscles remained normal.

189.—Knoop, F. Ueber den physiologischen Abbau der Säuren und die Synthese einer Aminosäure im Tierkörper. *Ztschr. physiol. Chem.*, 67, 1910, 489-502. Theory of oxidation of fatty acids through beta carbon atoms.

190.—Knudson, A. Relationship between cholesterol and cholesterol esters in the blood during fat absorption. *J. Biol. Chem.*, 32, 1917, 337-346. During digestion of fat (olive oil), cholesterol of blood showed no consistent change. Cholesterol esters increased in both plasma and corpuscles, but chiefly in corpuscles. Total fatty acids and lecithin likewise increased in plasma and corpuscles, but increase was greatest in corpuscles. Fairly constant relation between total fatty acids and cholesterol esters and between lecithin and cholesterol esters was noted in whole blood. Greater increase of cholesterol esters and lecithin in corpuscles, along with greater amount of fatty acids, indicates that corpuscles play very active part in fat metabolism. Refers to Iscovesco and also Terroine as claiming increase of cholesterol in blood after feeding cholesterol-free fat. Author finds (in his tables) rise of cholesterol esters in corpuscles from original 2 to 9 mg. to as much as 49 mg. per 100 cc. after feeding dogs 50 to 60 gm. olive oil alone.

191.—Knudson, A. Relationship between cholesterol and cholesterol esters in the blood during their absorption. *J. Biol. Chem.*, 45, 1921, 255-262. "Summary. A series of experiments carried out on dogs, feeding them cholesterol and cholesterol esters, respectively, shows that free cholesterol is increased considerably in all the experiments during the absorption of the diets, but that there is no apparent change in the amount of cholesterol in the ester form." Explanations are given for contrary results of Gardner and co-workers, Hueck and Wacker, and Mueller.

192.—Koch, Mathilde M., and Voegtlin, C. Chemical changes in the central nervous system as a result of restricted vegetable diet. Chemical changes in the central nervous system in pellagra. *Treas. Dept., U. S. Public Health Service*, Bulletin 103, 1916, pp. 135. (*Physiol. Abstracts*, 1, 1916, 308). Changes in lipoids are described, while proteins were little affected.

193.—Koch, W. Die Bedeutung der Phosphatide (Lecithane) für die lebende Zelle. *Ztschr. physiol. Chem.*, 63, 1909, 432-442. Lecithin solution can be used for imitating certain protoplasmic phenomena. Through formation of precipitation membranes and other properties, lecithin is probably an important factor in both chemical and pathological differentiation of cells.

194.—Kon, Y., and Yamada, H. Weitere Mitteilung über die experimentellen Studien der Lipoidstoffwechselstörungen. *Verhandlungen der Japanischen pathologischen Gesellschaft*, 6, 1916, 98-101. Vegetable diet with 5 gm. lanolin daily for 5 to 54 days caused lipoid deposits in various organs of rabbits. Phosphorus poisoning then resulted in deposit of only neutral fat in heart muscle, but of anisotropic droplets in convoluted tubules of kidneys. Rabbits survive intravenous injections of 0.3 to 9.5 gm. of lanolin in fine emulsion. Deposits in Kupffer cells and in endothelium of spleen are then demonstrable in five to fifteen minutes. The double refraction of deposited lanolin persists for some weeks and increases in sharpness.

195.—Krontowski, A., and Poleff, L. Ueber das Auftreten von lipoiden Substanzen in den Gewebskulturen und bei der Autolyse der entsprechenden Gewebe. *Zieglers Beiträge*, 58, 1914, 407-433. Fatty metamorphosis is distinguished from lipoid metamorphosis of cells in tissue cultures. Both were obtained more extensively in cultures under the influence of P and Ol. pulegii.

196.—Krylow, D. D. Experimentelle Studien über Nebennierenrinde. *Zieglers Beiträge*, 58, 1914, 434-467. Rabbits on lipoid-rich diets show marked hypertrophy and increase of lipoids of adrenal cortex, increasing with duration of the experiment. The histologic details are described.

197.—Kürten, H. Die Senkungsgeschwindigkeit der roten Blutkörperchen in ihrer Beziehung zu Cholesterin und Lecithin. *Arch. f. d. ges. Physiol.*, 185, 1920, 248-261. Stability of suspension of red blood corpuscles in their own plasma stands in relation to the ratio cholesterol-lecithin in whole blood. Cholesterol and lecithin act antagonistically: cholesterol hastens, lecithin inhibits sedimentation. The action of both is upon the red cells, probably upon the boundary surface between cell substance and plasma.

198.—Küttner, S. Ueber den Einfluss des Lecithins auf die Wirkung der Verdauungsfermente. *Ztschr. physiol. Chem.*, 50, 1906-7, 472-496. Finds that the action of both pancreatic and gastric juice is sometimes hastened, sometimes inhibited by lecithin, under unknown conditions as to cause.

199.—Kyes, P. Lecithin und Schlangengifte. *Ztschr. physiol. Chem.* 41, 1904, 273-277. Lecithin serves as an activator for the ambocepters of venom.

200.—Laignel-Lavastine, M. Disparition des enclaves lipocholestériques de le surrénale humaine dans l'agitation motrice. *C. r. soc. Biol.*, 81, 1918, 324-325. States the results observed in six cases.

201.—Lamb, F. W. The modifications undergone by fatty complexes in the alimentary mucosa. *Dublin J. Med. Sci.*, 144, 1917, 281-297. Principles and methods of differential staining of fatty substances are described in detail. Frogs were chosen for feeding experiments because of accuracy of observations possible after emptying intestine with mineral oil. Free fatty acids are not synthesized to neutral fats simultanously with their absorption into intestinal epithelium, but remain for a time demonstrable by the special stains. Saturated fats are partly unsaturated, or else mixed with unsaturated compounds in the cells. Cholesterol, derived from cells, food or bile, is believed to play an important part, because dyes show cholesterol so commonly present, and because cholesterol is able to neutralize the irritating effects of free fatty acids in feeding experiments. "The main conclusion is that the alimentary epithelium is the primary site of fat specialization. Althought fat foreign to the animal's body can be laid down in the fat depots, yet the vital activities of the cell endeavor rather to absorb fatty mixtures which resemble the fat peculiar

to the species or else to produce transformations which lead to this specialization."

202.—Landau, M. Nebenniere und Fettstoffwechsel. *Dtsch. med. Woch.*, 39, 1913, 546-549. Using methods like Kawamura's, the author finds increased lipoid content of the adrenal cortex in the most varied conditions which have in common only lipoid retention or increased lipoid formation. The opposite changes are accompanied by lipoid poverty of the adrenal. The adrenal lipoids in 7 cases of diabetes were sometimes high, sometimes low. With certain exceptions (inanition, infection) cholesterol esters behave like total lipoids of the adrenals. All the lipoids are probably stored by the adrenals from the blood. The function of the adrenal cortex is supposed to consist not in lipoid formation but in some correlation with the medulla, and indirectly with the sympathetic.

203.—Landau, M. Die Beziehungen der Nebenniere zum Cholesterinstoffwechsel. *Verh. d. dtsch. path. Gesellsch.*, 17, 1914, 144-149. The cholesterol content of the adrenals is said to vary with the visible esters. The adrenal cortex is an intermediate organ in cholesterol metabolism, but does not produce cholesterol and also does not esterize or deesterize it. Two-thirds of the cholesterol fed to a dog with thoracic duct fistula was found in ester form in the lymph; therefore the intestinal mucosa can form the ester. Excess cholesterol is taken up from the blood by the liver and is demonstrable in this organ before it appears in the bile. With the increase of blood cholesterol in epinephrectomized dogs, the Kupffer cells contain anisotropic lipoids, while the liver cells contain very little and the epitheium of the bile ducts and gall bladder contains none.

204.—Landau, M., and McNee, J. W. Zur Physiologic des Cholesterinstoffwechsels. *Zieglers Beiträge*, 58, 1914, 667-699. The lipoid content of human adrenals was low with phthisis and other infections, also with many neoplasms, and was high with contracted kidneys, atherosclerosis and cardiopathies. These changes pertained to the esters rather than to the free fat. The results of animal experiments (see above) are described.

205.—Landsberg, G. Das Lecithin, seine Rolle im Organismus und seine therapeutische Verwendung. *Zentralbl. f. d. ges. Physiol. u. Pathol. d. Stoffwechs.*, 1, 1906, 193-212. A review and bibliography of 203 references.

206.—Lapidus, H. Diastase und Handelslecithin. *Biochem. Ztschr.*, 30, 1910, 39-55. Commercial lecithin inhibited the diastase of saliva, pancreatic and intestinal juice, and also that of beef serum. The latter diastase is generally weakened by removal of lipoids by shaking out with ether, and is then restored by lecithin. The diastatic action of human serum is augmented by lecithin.

207.—Lattes, L. Sur la lipémie phlorizinique et sur ses rapports avec les migrations de graisse dans l'organisms. *Arch. ital. de biol.*, 53, 1910, 235-52. Principal conclusions are that fasting dogs have

slight increase of fat in blood, and that fasting phlorizinized dogs show a lipemia which may be three times the normal blood fat. This fat comes from the depots and represents an abnormal mobilization.

208.—Lattes, L. Ueber den Fettgehalt des Blutes des Hundes unter normalen und unter verschiedenen experimentellen Verhältnissen (Verdauung, Hungern, Phosphor-, Phloridzin- und Chloroformvergiftung). The petroleum ether extract (higher fatty acids and cholesterol) of dogs' serum (0.3 — 0.42%) was approximately doubled after fat feeding (0.45 — 0.76%). Slight increases were found in brief (3 day) fasts, but not in longer fasts (4-11 days). The existence of a "hunger lipemia" is questioned. After three of four days of phlorizin glycosuria with acetonuria, milky serum was observed once in twelve experiments, in which the percentages were 0.3 — 0.88. The rise is attributed to increased fat transport. P poisoned dogs showed 0.31 — 0.59% blood fat. Chloroform narcosis caused no increase.

209.—Lauber, H., and Adamük, V. Ueber das Vorkommen von doppelbrechendem Lipoid in der Netzhaut bei Retinitis albuminurica nebst Bemerkungen über die pathologische Anatomie dieser Erkrankung. *Arch. f. Ophthalmologie*, 71, 1909, 429-465. Lipoid deposits are one feature of albuminuric retinitis.

210.—Lehman, E. D. On the rate of absorption of cholesterol from the digestive tract of rabbits. *J. Biol. Chem.*, 16, 1914, 495-503. Conclusion: It is possible by giving rabbits small doses of cholesterol by mouth to demonstrate in the majority of instances an increase of this substance in the blood in the course of a few hours.

211.—Leo, H. Ueber die Giftablenkende Wirkung des Lezithins. *Dtsch. med. Woch.*, 46, 1920, 1045-1046. Clinical and experimental suggestions of neutralization of drugs (especially narcotics) by lecithin.

212.—Leva, J. Ueber alimentäre Lipämie. *Berl. klin. Woch.*, 46, 1909, 961-965. Confirmation of work of Neisser and Braeuning with dark field examination of hemoconia after fat meals, and comparison between different diseases.

213.—Levene, P. A. and Rolf, Ida P. Structure and significance of the phosphatids. *Physiol. Reviews*, 1, 1921, 327-393. Historical review and bibliography of lecithin, cephalin and sphingomyelin. Early hypotheses of role of lipoids in nervous disorders were overthrown by absence of chemical differences between brains of normal and insane persons. S. Fränkel's theory of differences between phosphatids of different organs was not substantiated. Various later hypothesis relate the phosphatids to tissue oxidation, membrane formation, structure of mitochondria, fat metabolism, and blood coagulation. Only cephalin is concerned in the latter. In hemolysis a cleavage product of lecithin is the active agent (Delezenne and Fourneau). MacLean disproved the claim that lecithin can function as a vitamine, showing that it acts thus only when impure.

214.—Lifschütz, J. Studien über den Ursprung und die Bildung des Cholesterins. *Ztschr. physiol. Chem.*, 55, 1908, 1-7. Possibility is shown chemically of synthesis of cholesterol from oleic acid. (No animal experiments).

215.—Lifschütz, J. *Ztschr. Physiol. Chem.*, 92, 1914, 383-401. Die Abbauprodukte des Cholesterins in den tierischen Organen (Gallensäuren). *Ztschr. physiol. Chem.*, 92, 1914, 383-401. Concludes that the bile acids may be regarded quantitatively as decomposition products of cholesterol.

216.—Loefer, M., and Verpy, G., Les dépôts de cholestérine dans certains arthropathies chroniques, *Progrès méd.*, 33, 1918, 221. The authors consider cholesterol as the irritant in certain joints where it is found in crystals, analogous to uric acid in gout.

217.—Lombroso, U. Sulla funcione del pancreas non segregante nell' intestino, nell' assorbimento alimentare. *Archivio di fisiologia*, 8, 1910, 209-238. (Review in *J. de physiol. et de path. gén.*, 12, 1910, 829). Pancreatic grafts secreting into the bowel are stated to influence digestion and absorption of food through some endocrine function.

218.—Lombroso, U. Kann das nicht in den Darm sezernierende Pankreas auf die Nährstoffresorption einwirken? *Arch. exper. Path. u. Pharm.*, 60, 1908, 99-114. Similar observations and conclusions.

219.—Lombroso, U. Action de l' acide chlorhydrique sur l'echange des graisses dans le foie survivant. *Archiv. internat. de physiol.*, 18, 1921, 484-494. The fasting liver does not possess the power of breaking down fat which is shown by the liver during digestion, but it acquires this power when HCl is injected into the stomach or duodenum. The livers of depancreatized dogs also lacked this power and did not acquire it after acid injection.

220.—Löwenthal, K. Zur Physiologie des Cholesterinstoffwechsels. Beziehungen zwischen Hoden und Cholesterinstoffwechsel. *Beitr. z. path. Anat. u. z. allg. Path.*, 61, 1915-16, 564-569. Contradicts the French view that cholesterol is secreted into the blood by organs like the adrenal and corpus luteum. Believes that lipoid of central nervous system is replaced for the adrenal medulla (derived from sympathetic) by cholesterol of adrenal cortex. The testis is added to Aschoff's series of organs of cholesterol metabolism. The cholesterolemia following epinephrectomy in rabbits is accompanied by an increase of cholesterol in liver and bile, but a decrease in the testicle; therefore, this is not a cholesterol storing organ. Bilateral, but not unilateral castration resulted in increase of blood cholesterol.

221.—Luden, Georgine. Observations on cholesterol retention as a factor in cell proliferation. *J. Lab* and. *Clin. Med.*, 1, 1915-16, 662-676. High blood cholesterol figures (0.254 — 0.710%) in tumor patients suggest relation of cholesterol retention to malignancy.

222.—Luden, Georgine. Observations on the changes in the cholesterol content of the blood of goats, following cholesterol feeding alone, Roentgen treatment alone, and cholesterol feeding combined with

Roentgen treatment and subsequent castration. *J. Biol. Chem.*, 27, 1916, 273-297. The blood cholesterol of goats (normal 0.186—0.216%) is increased by cholesterol feeding, castration, and probably pregnancy. It is reduced by diffuse Roentgen treatment, by anesthesia, and by a disease such as mange.

223.—Luden, Georgine. Studies on Cholesterol. III. The influence of bile derivatives in Bloor's cholesterol determination. *J. Biol. Chem.*, 29, 1917, 463-476. In 748 parallel determination by Bloor's original method with sodium ethylate, and the later modification without sodium ethylate, the former gave consistently lower values.

224.—Luden, G. Studies on cholesterol. III. Influence of bile derivatives in Bloor's cholesterol determination. *J. Lab. and Clin. Med.*, 3, 1917-1918, 93-109. The differences noted above are most marked in obstructive jaundice, and are attributed to bile.

225.—Luden, G. Studies on cholesterol. IV. Experiments concerning the relation of the diet, the blood cholesterol and the "lymphoid defense". *J. Lab. and Clin. Med.*, 3, 1917-18, 141-174. Concludes that a diet which increases cholesterol weakens the lymphoid defense, and vice versa.

226.—Luden, G. Studies on cholesterol. VI. The value of blood cholesterol determinations, and their place in cancer research. *J. Lab. and Clin. Med.*, 4, 1919, 719-735. Cholesterol metabolism is influenced by basal metabolism; e. g. an inverse relationship is found in myxedema. Other modifying factors are diet, radium treatment, infections and hemorrhage. An intimate relation exists between lawless proliferation of cells and disturbances of cholesterol metabolism.

227.—Luden, G. The blood cholesterol, its importance and the value of its determination in cancer research. *Canad. Med. Assoc. J.*, 12, 1922, 147-152. Refers to Dezani's findings that mice died on cholesterol-free diets after apparently synthesizing cholesterol for a short time, and other literature on cholesterol synthesis. Cholesterol inhibits bacterial growth. It is generally found high in the blood in acute infections and low in chronic infections, such as tuberculosis and syphilis. The findings with gallstones are variable. Blood cholesterol can be reduced by a diet of milk, fruit and vegetables. The increase resulting from cholesterol-poor food such as meat and oatmeal is attributed to the bile and pancreatic juice. Various experimental and clinical observations link tumor growth with hypercholesterolemia.

228.—Lutz, W. Ueber grosszellige Hyperplasie der Milzpulpa bei diabetischen Lipämie. *Zieglers Beiträge*, 58, 1914, 273-284. Description of clinical cases.

229.—Lyman, J. F. Metabolism of Fats. I. Utilization of palmitic acid, glyceryl palmitate, and ethyl palmitate by the dog. *J. Biol. Chem.*, 32, 1917, 7-11. The emulsified esters of fatty acids are not absorbed as such, but absorption is limited by rate of hydrolysis. Lyman, J. F. Metabolism of fats. II. The effect of feeding free palmitic acid, glyceryl palmitate, and ethyl palmitate on the

depot fat in the white rat. *J. Biol. Chem.*, 32, 1917, 13-16. After feeding free palmitic acid, glyceryl palmitate or ethyl palmitate to white rats, essentially the same kind of fat is stored in the fat depots and it consists largely of tripalmitin. Neither free palmitic acid nor ethyl palmitate is deposited unchanged. Fat deposited with fat-poor diet differs markedly from that laid down when diets contain palmitic acid or its esters.

230.—Mac Callum, W. G. (Arteriosclerosis). *Physiol. Reviews*, 2, 1922, 70-91.

231.—MacLean, H. The composition of "lecithin", together with observations on the distribution of phosphatids in the tissues and methods for their extraction and purification. *Biochem. J.*, 9, 1915, 351-378.

232.—Magnus-Levy, A., and Meyer, L. Die Fette im Stoffwechsel. *Carl Oppenheimer's Handbuch der Biochemie des Menschen und der Tiere.* Vol. 4, Jena, 1911, 445-488. Review and bibliography of fat metabolism. Slight lipemia has been described in poisoning with phlorizin, narcotics, etc. and in clinical conditions such as pregnancy, nephritis, obesity, dyspnea, pneumonia, esophageal cancer, chronic alcoholism, and diabetes. Marked lipemia may be absent even in the severest diabetic acidosis or coma. Explanations are uncertain, but diabetic lipemia probably represents a gradual accumulation of fat which is somehow impeded in leaving the blood vessels.

233.—Majolo, B. La colesterina del sangue umano in diversi stati morbosi. *Folia med.* (Napoli), 6, 1920, 505-9; 606-13; 705-11; 729-35. Analyses by Bloor's method, with findings similar to those of other authors in a series of diseases.

234.—Malerba, G. L. Il tasso colesterinico del siero di sangue in varie forme morbose. *Riforma med.*, 37, 1921, 602-605. Normal serum cholesterol is regarded as 0.12 — 0.18 percent. The findings are normal in heart disease and acute nephritis; high in chronic nephritis, diabetes, liver and gall-bladder disease; low in acute febrile infections, asthma, epilepsy and pernicious anemia. Oral administration of cholesterol in two cases of pernicious anemia had little influence upon the serum cholesterol.

235.—Mansfeld, G. Studien uber die Physiologie und Pathologie der Fettwanderung. *Pflüger's Arch.*, 129, 1909, 46-62. Normal dog blood and liver each yields only about half its fat to ether extraction, supposedly because of a fat-albumin compound. In P poisoning this normal combined fat of the liver becomes free, and can be extracted with ether.

236.—Marinesco, G., and Parhon, L' influence de l'ablation de l'appareil thyro-parathyroidien sur la graisse surrénal. *C. r. soc. Biol.*, 64, 1908, 768-769. The adrenal cortex is supposed to secrete lipoids and to be perhaps one of the lecithin forming organs.

237.—Marriott, W. McK., and Sisson, W. R. Variations in the lipoid ("fat") content of the blood of infants under certain nutritional conditions. *Amer. J. Dis. Child.*, 16, 1918, 75-82. The blood fat

of infants is found independent of the state of health or nutrition, but is perhaps an index of the "nutritional trend", as infants gaining weight generally show higher blood fat than those stationary or losing weight.

238.—Mayer, A., and Terroine, E. F. Sur les jecorines naturelles et artificielles. *C. r. soc. Biol.*, 62, 1907, 773. The natural and artificial jecorins are supposed to consist of albumin, lecithin and dextrose.

239.—Mayer, A., Mulon, P., and Schaeffer, G. Contribution a la microchemie des surrénales. *C. r. soc. Biol.*, 73, 1912, 313-18. The fat or lean adrenal cortex is considered characteristic of different animal species.

240.—Mayer, Paul. Ueber Lecithinzucker und Jekorin, sowie über das physikalisch-chemische Verhalten des Zuckers im Blut. *Biochem. Ztschr.*, 1, 1906, 81-107. Natural and artificial jecorins are described. The blood sugar is believed to occur free, not in lecithin combination. Jecorin activates cobra venom, and hemolysis is quicker than with lecithin activation.

241.—Mayer, P. Ueber Blutjekorin und uber das physikalisch-chemische Verhalten des Zuckers im Blut., *Biochem Ztschr*, 4, 1907, 545-553. Differences are found between jecorins from different organs. Little if any blood sugar is combined in the form of jecorin.

242.—Meigs, E. B., Blatherwick, N. R., and Cary, C. A. Contributions to the physiology of phosphorus and calcium metabolism in relation to milk secretion. *J. Biol. Chem.*, 37, 1919, 1-75. Analyses of blood from jugular and mammary veins of cows indicate that the mammary glands take up phosphatid from the blood and convert it into milk fat and inorganic phosphate. A similar hypothesis is suggested for the fat metabolism of muscles and tissues in general.

243.—Meyerstein, W. Ueber die Beziehungen von Lipoidsubstanzen zur Hämolyse. *Arch. exp. Path. u. Pharm.*, 62, 1910, 258-265. Hemolysis by venom, soap, etc. is inhibited by certain lipoids, especially cholesterol.

244.—Minami, D. Ueber den Einfluss des Lecithins und der Lipoide auf die Diastase (Amylase). *Biochem. Ztschr.*, 39, 1912, 355-380. Contrary to Bang, diastase is found to be entirely independent of lipoids.

245.—Minz, A. Ueber Toxolecithide. *Biochem. Ztsch.*, 8, 1909, 357-381. Cholesterol inhibits hemolysis by withdrawing the toxolecithid from its solutions.

246.—Mohr, (discussion on oat cure). *Kong. f. inn. Med.*, 1911, p. 253. Fatty liver is believed to result from a combination of degeneration and infiltration.

247.—Mottram, V. H. Fat infiltration of the cat's kidney. *Proc. Am. Soc. Biol. Chemists*, 24, 1916, XI-XII.

248.—Mottram, V. H. Fatty infiltration of the cat's kidney. *J. Physiol.*, 50, 1916, 380-390. According to theory of Leathes (Lan-

cet, 1909, p. 593) the iodin value of the liver fatty acids should lie between that of the fat depot acids (as lower limit) and that of the heart or kidney fatty acids (as upper limit). Such a result was found in author's previous work with Coope (*J. of Physiol.*, 49, 1915, 157) but exceptions were present in cat's kidneys reported by Leathes. Present work shows variable iodin values for fatty acids of kidneys of cats on fixed diet for a month or more. But average iodin value is lower (i. e. fatty acids are more saturated) in kidney than in depots, and still more so than in liver. From microscopic appearance, author concludes that cat kidney cells readily become infiltrated with circulating fat derived from the food, in this case milk-fat. This peculiarity explains difference from the findings in rabbits.

249.—Müller, J. Ueber Maskierung des Blutfettes und der Blutlipoide sowie über Verdauungslipämie beim Menschen. *Zischr. physiol. Chem.* 86, 1913, 469-483. Description of a case of nephritis with 40-50 gm. albumin daily in urine and chylous hydrothorax. The blood was opaque with fat, which could not be seen as globules microscopically or removed by centrifuge or ether or colored by osmic acid. The petroleum ether extract of the serum amounted to 3.18 —3.56 percent, cholesterol 0.682 — 0.836 percent, lecithin 0.688%. A later serum, shortly before death, appeared clear, yet contained 1.11 percent total ether extract, 0.28% cholesterol and 0.176% lecithin. Retention of food fat in the blood was considered improbable because this patient had been several months on milk diet, poor in lipoids.

250.—Mueller, J. H. The cholesterol melabolism of the hen's egg during incubation. *J. Biol. Chem.*, 21. 1915, 23-28. The cholesterol of hen's eggs is practically all free up to the thirteenth day of incubation. Thereafter esterification occurs, until at hatching over 40 percent is in ester form. The author favors Hanes' suggestion that cholesterol may serve to distoxicate fatty acids by combining them into harmless esters.

251.—Mueller, J. H. The mechanism of cholesterol absorption. *J. Biol. Chem.*, 27, 1916, 463-480. Cholesterol is readily absorbed from the intestinal tract and can be demonstrated in thoracic duct chyle. When free cholesterol is fed a portion is found esterified. The proportion in the chyle is about the same if cholesterol esters are fed (one part free to two or three combined), so that processes of hydrolysis and esterification must occur in the mucosa or elsewhere. The ratio seems not to be affected by small quantities of free fatty acids in the food.

252.—Mueller, J. H. The mechanism of cholesterol absorption. *J. Biol Chem.*, 27, 1916, 463-480. Cholesterol absorption is impaired by tying either the bile or pancreatic duct, indicating an important role of both juices. Cholesterol oleate was not hydrolyzed by either of them. Minced intestinal mucosa or mesenteric lymph glands showed no action on cholesterol. Cholesterol is believed to be esterified by the agency of pancreatic juice. The theory is favored

that one function of cholesterol is to distoxicate fatty acids in the body by combining them into esters.

253.—Mulon, P. Disparition des enclaves de cholestérine de la surrénale au cours de la tetanisation faradique ou strychnique. *C. r. soc. Biol.*, 75, 1913, 189-192. Prolonged tetanization of frogs with strychnine or faradic current, or of rabbits with faradic current for several days resulted in extensive or complete disappearance of lipoid from the adrenal cortex.

254.—Munk, I. Der Einfluss des Glycerins, der flüchtigen und festen Fettsäuren auf den Gaswechsel. *Pflügers Arch.*, 46, 1890, 303-334. Higher fatty acids (oleic) are much more toxic than lower acids (butyric) when given intravenously. But a dog on protein-fat diet is said to have remained in equilibrium when fatty acids were substituted for the fat.

255.—Munk, I. Ueber die Wirkungen der Seifen im Thierkörper. *Arch. f. Physiol.*, 1890, 116-141. Intravenous injection of 0.11 or 0.13 gm. of oleic acid per kg. kills rabbits or dogs by heart paralysis. The lower toxicity when the injection is given into a branch of the portal vein is supposed to indicate a retaining or distoxicating function of the liver.

256.—Murlin, J. R., and Riche, J. A. Blood fat in relation to heat production and depth of narcosis. *Proc. Soc. Exp. Biol and Med.*, 13, 1915, 7-8. Blood fat falls in proportion to depth of narcosis produced by chloretone or morphine. Increase of fat in blood by injection of 3% emulsion of lard oil causes lowering of respiratory quotient and increase of heat production.

257.—Murlin, J. R., and Riche, J. A. The fat of the blood in relation to heat production, narcosis and muscular work. *Proc. Am. Phys. Soc.*, Dec. 1915. *Am. J. Physiol.*, 40, 1916, 146, Exercise causes first a decrease of blood fat, then an increase by the end of an hour. After an hour's rest the percentage returns to or below the usual figure. The fluctuations are greater in fat than in lean dogs.

258.—Myers, V. C., and Wardell, E. L. The colorimetric estimation of cholesterol in the blood, with a note on the estimation of cholesterol in feces. *J. Biol. Chem.*, 36, 1918, 147-156. Describes method, giving good checks with digitonin method (0.077 to 0.164% in various bloods) against higher values by Bloor method (0.095 — 0.206).

259.—Myers, V. C. Chemical changes in the blood in disease. VI. Cholesterol. *J. Lab and Clin. Med.*, 5, 1919-20, 776-783. Review and bibliography.

260.—McAuliff, G. R. Hypertrichosis, variations in female secondary sexual characteristics, and internal secretions. *J. Amer. Med. Assn.*, 66, 1916, 15-17. Report of a case of dermoid cyst of ovary with hypertrichosis. The condition is regarded as a pluriglandular disorder in which the adrenal is the most important but other organs play a part.

261.—McClure, C. W., Vincent, B. and Pratt, J. H. Metabolism studies

on dogs with subcutaneous pancreatic grafts. *Abstract of Proceedings of the Eighth Annual Meeting of the American Society for Clinical Investigation*, 1916, 34-76. Contrary to Lombroso, subcutaneous pancreatic grafts had no influence upon digestion and absorption.

262.—McCrudden, F. H. and Sargent, C. S. Comparison of the glucose and cholesterol content of the blood. *J. Biol. Chem.*, 33, 1918, 387-389. Analyses on 36 individuals in normal and various diseased conditions showed blood sugar 0.086 — 0.204 and cholesterol 0.132 — 0.226%, with no consistent relationship between them.

263.—McIntosh, W. A. Histological study of fat contained in the mucosa of the alimentary tract of moderately starved cats. *Amer. J. Physiol.*, 46, 1918, 570-583. Cats starved 24 to 48 hours showed stainable fat globules in gastric and intestinal mucosa and submucosa and intestinal glands. These appearances may represent phases of metabolism of the epithelial cells and should not be confused with fat absorption.

264.—McKibben, P. S. A note on intravascular fat with relation to the experimental study of fat embolism in "shell-shock". *Amer. J. Physiol.*, 48, 1919, 331-339. Free fat droplets are demonstrable by staining in blood vessels of brain, lungs and other organs of dog and rabbit in considerable numbers, less numerously in the cat. They may be increased by fat feeding but are not altered by shock.

265.—McMeans, J. W. The accumulation of anisotropic fats in the interstitial cells of the kidney. *J. Med. Research*, 33, 1916, 475-479. Rabbits were given cholesterol by stomach tube in olive oil or sodium oleate emulsion in dosage of 0.26 — 0.56 gm. daily, up to maximum of 75 gm. in 19 days. The changes in aorta and adrenals were variable and not parallel to dosage. In the kidneys, proliferation of cells and small capillaries in interstitial tissue of pyramids was first noticed. The most advanced stage showed islands of cells of various shapes growing between the tubules and compressing them. These endothelial cells were filled with Sudan-staining anisotropic globules, and resembled atheromatous plaques in aorta. Smaller quantities of lipoids were found in the endothelium of capillaries and the epithelium of some tubules. Also, in three rabbits there was proliferation of cells in the cortex, evidently originating from the lining cells of the tubules.

266.—McMeans, J. W. Tissue reactions in experimental hypercholesterolemia. *J. Med. Research*, 33, 1916, 481-491. Hypercholesterolemia resulted in swelling of rabbit adrenals with lipoids, till after 166th day they were as much as 2 cm. in diameter, by reason of widening of the cortex with little change in the medulla. The chief site of cholesterol storage was the liver. The Kupffer cells were prominent and apparently passed on the lipoid to adjacent liver cells. In extreme cases the spleen was enlarged to twice normal size and its sinuses were filled with large cells resulting from proliferation of lining endothelium. Two rabbits pregnant during the feeding had ovaries almost entirely occupied by luteal tissue,

leaving only a small rim of ovarian tissue containing Graafian follicles. The intima of the aorta and the pulmonary artery and the endothelia of some smaller arteries and arterioles showed proliferation, foam cells, anisotropic lipoids and cholesterol clefts, and fibroblastic increase with splitting of internal elastic layers and development of new elastic fibres. The pictures are interpreted as successive overloading of the cholesterol capacity of different organs.

267.—MacNee. Beiträge sur Frage des Cholesterin-Stoffwechsels und der Cholesterinausscheidung. *Dtsch. med. Woch.*, 39, 1913, 583-584. Intraperitoneal injections of cholesterol resulted in its accumulation not only in the abdominal cavity but also in cells, and an increase in blood cholesterol. The cholesterol content of the bile of pregnant women was normal.

268.—Nakamura, T. Ueber die Bestimmungsmethode für das Fett im Blute. *Mitt. d. med. Gesellsch. zu Tokyo.*, 33, 1919, No. 20, 1.

269.—Neilson, C. H., and Wheelon, H. Studies on the resistance of the red blood cells. III. The relation of cholesterol to the resistance of the red cells to the hemolytic action of saponin. *J. Lab. and Clin. Med.*, 6, 1921, 568-578. The authors conclude that the cholesterol in and about cells acts as an antihemolytic, while lecithin tends to combine with toxins to form lecithids. Diseases with high cholesterol content show increased red cell resistance to sapotoxin; diseases with low cholesterol show lessened resistance to hemolytic agents.

270.—Neisser, E. and Derlin, L. Ueber Lipämie. *Ztschr. klin. Med.*, 51, 1904, 428-438. Description of an emaciated diabetic, dying in coma with 19.71% ether extract of blood and 0.8% fat in urine. From the iodin and Reichert-Meissl numbers it is concluded that the blood fat came from the food fat.

271.—Neisser, E., and Braeuning, H. Ueber Verdauungslipämie. *Ztschr. exper. Path. und Therap.*, 4, 1907, 747-760. The serum of men and animals (except the rabbit) becomes more or less cloudy with hemoconia during fat digestion. The clear serum still contains fat in some invisible combination.

272.—Nerking, J. Ueber Fetteiweissverbindungen. *Pflügers Arch.*, 85, 1901, 330-344. Peptic digestion reveals fat in horse serum not removable by Soxhlet extraction.

273.—Novi, I. Etudes pharmacologiques sur la lécithine. *Arch. ital. de biol.*, 69, 1919, 48-54. The lipoids of dogs' brains are found diminished by about two percent after death from ether or chloroform anesthesia. The brains after anesthesia contain more phosphatids and less fat and cholesterol. Different results are described from the intravenous injection of brain lipoid from normal dogs and dogs killed with anesthesia. The intravenous injection of fatal quantities of distilled water produces changes in the brain lipoids. References are given to show antagonistic action of lecithin and cholesterol on phagocytosis.

274.—Osborne, T. B., and Mendel, L. B. Feeding experiments with

fat-free food mixtures. *Proc. Soc. Exp. Biol. and Med.*, 9, 1912, 73. The authors made rats grow at normal rates on mixtures containing only purified proteins, carbohydrates and inorganic salts.

275.—Osborne, T. B., and Mendel, L. B. Beobachtungen über Wachstum bei Fütterungsversuchen mit isolierten Nahrungssubstanzen. *Ztschr. physiol. Chem.*, 80, 1912, 307-370. Experiments show growth on fat-free diets, in oppositions to Stepp.

276.—Osborne, T. B., and Mendel, L. B. Feeding experiments with fat-free food mixtures. *J. Biol. Chem.*, 12, 1912, 81-89. Normal growth is described on fat-free diets.

277.—Osborne, T. B., and Mendel, L. B.—The relation of growth to the chemical constituents of the diet. *J. Biol. Chem.*, 15, 1913, 311-326. The above mentioned growth on fat-free diets extended only to a certain point and stopped. Some element in cream is here shown necessary for permanently successful growth.

278.—Osborne, T. B., and Mendel, L. B. Growth on diets poor in true fats. *J. Biol. Chem.*, 45, 1920, 145-152. Literature and opinions on fat-poor diets. The authors demonstrate growth in rabbits on purified diets with additions of vitamines, and conclude "if true fats are essential for nutrition during growth the minimum necessary must be exceedingly small."

279.—Pacini, A. J. Blood cholesterol in pernicious anemia. *American Medicine*, 24, 1918, 92-94. Gives table, showing normal cholesterol in whole blood 150 mg. per 100 cc., in serum 160 mg., in cells 140 mg.; ratio 55:40. In 16 cases of pernicious anemia, cholesterol in whole blood was 70 to 140 mg.; in serum 20 to 60 mg, in cells 45 to 110 mg., ratios 55:68 to 55:261. The author treats anemia patients with lanolin inunctions.

280.—Pacini, A. J. Blood cholesterol. *Medical Record*, 94, 1918, 441-446. The author finds increase of cholesterol in only a part of his cases of gallstones, and suggests that many of the published elevations may be due to bile, representing an "occult jaundice". The distribution is found changed, however, in that cholesterol is increased in plasma and decreased in corpuscles in gallstone cases.

281.—Peritz, G. Zur Pathologie der Lipoide. *Ztschr. exper. Path. u. Therap.*, 8, 1910-11, 255-278. A deficiency of lecithin is claimed in diabetes, syphilis, and especially in nervous diseases, and lecithin injections are recommended.

282.—Porak, R. Corrélation de la cholestérinémie et du pronostic dans certains conditions cliniques et expérimentales. In a previous report the author found hypercholesterolemia attended with a grave prognosis in malaria. He now finds a fall of blood cholesterol in early syphilis, and a rise under treatment. Choresterol was little changed in mild grippe, lowered in severe cases, but sometimes normal in fulminant cases. Operations under ether or chloroform did not alter blood cholesterol in human patients, but a fall occurred in two dogs chloroformed three or four hours. Blood from a suprarenal vein is said to lake very quickly and to contain less cholesterol than arterial or jugular vein blood.

283.—Porges, O., and Neubauer, E. Physikalisch-chemische Untersuchungen über das Lecithin und Cholesterin. *Biochem. Ztschr.*, 7, 1907-8, 152-177. Jecorin or lecithin glucose is a mere mixture.

284.—Pratt, J. H., Lamson, P. D., and Marks, H. K. The effect of excluding pancreatic juice from the intestine. *Trans. Assn. Amer. Phys.*, 24, 1909, 266-281. Complete exclusion of pancreatic juice greatly impaired digestion and absorption in dogs.

285.—Pribram, H. Beitrag sur Kenntnis des Schicksals des Cholesterin und der Cholesterinester im tierischen Organismus. *Biochem. Ztschr.*, 1, 1906, 413-424. Brief cholesterol feeding (3 gm. on a single day, or a total of 5 gm. or less over several days) increased blood cholesterol in rabbits from normal of 0.029-0.0275 per cent to 0.11-0.158 per cent.

286.—Quinan, C. Lipase Studies. I. On the ester splitting faculty of normal tissues. *J. Med. Research*, 27, 1915, 45-71. The same lipase is believed to be present in liver, kidney and muscle of normal guinea pig, in quantities perhaps proportionate to their cellularity. The influence of lecithin or cholesterol was negative.

287.—Reicher, K. Zur Kenntnis des Fett- und Lipoidstoffsechsels. *Verh. d. dtsch. Kong. f. inn. Med.*, 28, 1911, 327-330. Fat-protein compounds represented only five to ten percent of the total blood fat, 3 to 26 hours after fat feeding. Hagenau is said to have found marked increase of lecithin and cholesterol after feeding pure triolein. The increase of cholesterol is in the form of esters. The liver is believe to manufacture lecithin and cholesterol from fats, as perfusion of surviving dog livers with addition of triolein caused great increase of lecithin and cholesterol in the perfusate. Loew 20 years previously advanced the theory that fat utilization occurs through the stage of lecithin.

288. Reicher, Fett- und Lipoidstoffwechsel bei Diabetes mellitus. *Verh. d. dtsch. Kong. f. inn. Med.*, 30, 1913, 155-158. In normal human blood, total fat is about 0.5 percent, of which about 0.09 percent is lecithin and cholesterol esters. After ingestion of fat practically free from lipoids, not only neutral fat but also the lipoids are increased in blood, up to 80 percent. Total fat in digestion lipemia is perhaps 0.9 percent, of which two-thirds is lecithin and cholesterol esters. During this increase the R. Q. indicates fat combustion. Facts indicate that lecithin and cholesterol facilitate combustion of fatty acids. Analogy is drawn with plants, where the more intense fat combustion in germination is accompanied by doubling of lecithin content. Also in the fat mobilization of anemia, P poisoning, fasting and narcosis, as in alimentary lipemia, an increased proportion of the increased total fat is lecithin and cholesterol esters. In diabetes with advanced acetonuria, the fasting blood fat is about the level of normal alimentary lipemia, perhaps 0.8%, and nearly two-thirds again is lecithin and cholesterol. The rise in digestion is slower but reaches a greater height, perhaps 1.43%; and again a high proportion is lecithin and cholesterol esters, which perhaps reach 1.03%. The author mentions

similar observations of himself and Stein concerning blood sugar in diabetes. Both carbohydrate and fat metabolism show a slowing or delay. In less advanced diabetes the fat disturbance is less marked. There is a double cause for the lipemia; First, increased fat mobilization; second, a disorder of fat metabolism. When this disturbance is not too severe, after fat combustion there is a fall of blood fat below the normal fasting values. But if the disease advances to coma, there are crests and valleys of waves, but never a fall to normal blood fat values.

289.—Reiman, S. P., and Magoun, J. A. T. The cholesterol content of the blood in gallstone disease. *Surg., Gynec., Obstet.*, 26, 1918, 282-284. The authors adopted 200 mg. per 100 cc. as the upper normal limit of blood cholesterol. Gallstone cases in Deaver's service averaged 219 mg.; diseases of gall bladder requiring removal, 199.9 mg; cases without gallstones, 215 mg.; various right upper abdominal lesions 229 mg. The averages were higher in women than in men. Obstructive jaundice gave high figures. The highest level was 447 mg. with carcinoma of head of pancreas, and the lowest 111 mg. in chronic cholecystitis with stones. Cholesterol determinations therefore were not a diagnostic aid.

290.—Rémond and Rouzaud. L'azotémie et la cholestérinémie chez les migraineux. *Rev. de méd.*, 38, 1921, 97-112. Elevation of plasma cholesterol to 210 mg. is reported in migraine, as against 160 mg. per 100 cc. regarded as normal.

291.—Resch, A. Lipase und Lymphocyten. *Dtsch. Arch. klin. Med.*, 118, 1915, 179-189. The lipolytic enzyme in an exudate produced by intrapleural injection of lecithin is derived from lymphocytes.

292.—Rewald, B. Der Cholesteringehalt normaler und pathologischer menschlicher Organe. *Biochem. Ztschr.*, 99, 1919, 253-260. Cholesterol analyses of bone-marrow, liver, kidneys and brain were found not diminished in diabetic lipemia. Therefore, the excess of circulating cholesterol was not derived from these organs. (It seems more striking that there is found no increase in lipoid in these organs in lipemic cases with 0.52 or 2.16% serum cholesterol).

293.—Richter-Quittner, M. Ueber die Verteilung des Cholesterins und seiner Ester auf Blutkörperchen und Plasma unter physiologischen und pathologischen Verhältnissen. *Wien. Arch. f. inn. Med.*, 1, 1920, 425-454. Reference is made to claims of Falta and the author that in blood drawn with sufficient care the corpuscles are free from sugar, chlorine, and non-protein nitrogen, both in normal cases and in those with pathological elevation of these substances in the plasma. Total cholesterol is found uniformly distributed between plasma and cospuscles normally and in alimentary and pathological hypercholesterolemia, with a few slight exceptions in favor of the plasma in pathological cases. The corpuscles of man and all species examined (horse, cow, dog, cat, rabbit) contain only free cholesterol and no esters, while the plasma cholesterol is normally all in the form of esters. The feeding of fat, cholesterol-

rich diet or pure cholesterol increases both free and combined cholesterol in the blood, the esters rising first and equilibrium occurring within a few hours, while all cholesterol is apparently saponified as it enters the corpuscles. In pathologic hypercholesterolemia only the free form is increased, and much free cholesterol may occur in the plasma with small quantities of esters.

294.—Riddle, O., and Harris, J. A. Note on the relation of blood fat to sex, and on the correlation between the blood fat and egg production in the domestic fowl. *J. Biol. Chem.*, 34, 1918, 161-170. The blood of actively laying hens is higher in fat and phosphorus than that of non-laying hens.

295.—Robertson, T. B. and Burnett, T. C. Preliminary communication on the part played by cholesterol in determining the incidence of carcinoma. *Proc. Soc. Exper. Biol. and Med.*, 10, 1912-13, 140-143. Milk-fed rats showed a slightly lowered proportion of "takes" on implantations of Flexner-Jobling carcinoma.

296.—Robertson, T. B., and Burnett, T. C. The influence of lecithin and cholesterin upon the growth of tumors. *J. Exper. Med.*, 17, 1913, 344-352. Cholesterol, suspended in dilute alcohol or sodium oleate, injected into tumors caused acceleration of primary and metastatic growths. Lecithin injections diminished metastases and sometimes retarded the primary growth.

297.—Robertson, T. B. The influence of cholesterol upon the growth of the white mouse. *J. Biol. Chem.*, 25, 1916, 635-646. Cholesterol first retarded then accelerated growth, and increased variability. Aortic lesions, as found in rabbits, were not observed.

298.—Robertson, T. B. The influence of lecithin upon the growth of the white mouse. *J. Biol. Chem.*, 25, 1916, 647-661. Lecithin feeding did not affect growth of mice, contrary to results reported with subcutaneous injections and in lower organisms. Cholesterol fed to mother retarded growth of suckling mice.

299.—Robertson, T. B. Experimental studies on growth. VIII. The influence of a diet deficient in fats and of the same diet with cholesterol added, upon the growth of the white mouse. *J. Biol. Chem.*, 27, 1916, 393-402. Fat-free diets produced fatal disturbances of health, which were not prevented by addition of cholesterol.

300.—Robertson, T. B. Recent investigations on the influence of the anterior lobe of the pituitary body upon growth, and on the properties of the growth-controlling constituent, tethelin. Endocrinology, 1, 1917, 24-37. Tethelin is characterized as a lipoid.

301.—Robertson, T. B. The growth and senescence of white mice fed upon pituitary (anterior lobe) tissue, tethelin, egg lecithin, or cholesterol. *J. Biol. Chem.*, 37, 1919, 393-426. The effects of the various feedings were transitory or negative.

302.—Roger, H., and Binet, L. Lipolytic power of blood and tissues. *C. r. soc. Biol.*, 86, 1921, 79-80, 203-204. The lipolytic power of other organs is much less than that of the liver, lungs, and lymph glands, which supposedly act upon the fat-rich lymph. Lipolytic

power in right heart-blood is slight or absent, and is slightly raised by aeration, but not as high as that of arterial blood. In passing through the lungs the red corpuscles gain a power of splitting fat which is not conferred by simple aeration.

303.—Rogozynski, F. Beiträge zur Kenntnis des Phosphorstoffwechsels im tierischen Organismus. *Malys Jahresber.*, 40, 1910, 595-597. It is concluded that lecithin is absorbed after splitting in the bowel, because no increase of organically bound P was found in the liver after lecithin feeding. Nitrogen metabolism was not affected.

304.—Rona, P., and Michaelis, L. Ueber Ester- und Fettspaltung im Blute und im Serum. *Biochem. Ztschr.*, 31, 1911, 345-354. Delicate surface tension observations show a splitting of monobutyrin by a serum ferment.

305.—Rosenberg, S. Ueber den Einfluss des Pankreas auf die Resorption der Nahrung. *Pfügers Archiv.*, 70, 1893, 371-449. Removal of the pancreas impaired digestion and absorption of food to a far greater degree than ligation of its ducts.

306.—Rosenfeld, G. Ueber Phloridzinwirkungen. *Verh. d. dtsch. Kong. f. inn. Med.*, 12, 1893, 359-366. Phlorizin fatty liver is prevented by carbohydrate. A fatty infiltration as opposed to degeneration is proved by the fact that when the adipose tissue of a dog has been filled by previous feeding with a foreign fat, upon phlorizination this foreign fat is found in the liver.

307.—Rosenfeld, G. Fettbildung. *Ergebnisse d. Physiol.*, 2. (1) 1903, 50-94. Antagonism between fat and glycogen in the liver is emphasized.

308.—Rosenfeld, G. Fett und Kohlenhydrate. *Berl. klin. Woch.*, 1906, 978-981. Similar observations and theories.

309.—Rosenfeld, G. Fett und Kohlenhydrate. *Berl. klin. Woch.*, 43, 1906, 978-981. Carbohydrate is the kindling for fat combustion.

310.—Rosenfeld, G. Eiweisskörper und Leberverfettung. *Berl. klin. Woch.*, 47, 1910, 1268-72. Protein, through its carbohydrate compotent prevents fatty liver.

311.—Rosenthal, F. Ueber Cholesterinverarmung der menschlichen roten Blutkörperchen unter dem Einfluss der Kriegsnährung. *Dtsch. med. Woch.*, 45, 1919, 571-573. In 16 undernourished, otherwise healthy Germans in wartime, corpusele cholesterol was found 0.0573-0.0124%, as compared with figures for normal corpuscles of 0.040-0.053% by Henes and 0.050-0.66% by Authenreith- Funk. Contrary to authors who assert that cholesterol in corpuscles is entirely free, the author finds an appreciable portion in the form of esters.

312.—Rosenthal, F. and Patizek, F. Ueber Cholesterinverarmung des Blutes unter dem Einfluss der Kriegsernährung. *Berl. klin. Woch.*, 56, 1919, 793-796. A table shows standards fixed by previous authors for normal serum cholesterol ranging from 0.11-0.24 per cent. The present writers find 0.135-0.205% in well nourished persons. In 22 undernourished Germans the serum cholesterol ranged from 0.226% maximum to 0.0337% minimum. All but 4 were below 0.11%.

These changes in both serum and corpuscles are attributed to lipoid-poor diet, which is considered likely to reduce the resistance to tuberculosis.

313.—Rosenthal, H., and Trowbridge, P. F. The estimation of fat. *J. Biol. Chem.*, 20, 1915, 711-717. Description of a modified saponification method.

314.—Rothschild, M. A. Zur Physiologie des Cholesterinstoffwechsels. III. Die Beziehungen der Nebenniere zum Cholesterinstoffwechsel. *Beitr. z. path. Anat. u. allg. Path.*, 60 1914-15, 39-65. Hypercholesterolemia following unilateral or bilateral epinephrectomy proves that this excess is not derived from the adrenals. The increase of esters also disproves any supposed esterizing function of the adrenals. Addison's disease is believed to represent a disturbance of the relation between cortex and medulla.

315.—Rothschild, M. A. Zur Physiologie des Cholesterinstoffwechsels. IV. Ueber die Beziehungen der Leber zum Cholesterinstoffwechsel. *Beitr. z. path. Anat. u. allg. Path.*, 60, 1914-15, 66-75. Cholesterol is increased in the blood, liver and bile of epinephrectomized dogs. The deposits of cholesterol esters in the Kupffer cells resemble those after cholesterol feeding. The liver is the natural regulator of cholesterol metabolism, and the content of the bile merely reflects that of the blood in different species. Even with high cholesterol in blood, liver and bile, the epithelium of the gall bladder and ducts contains very little; therefore this epithelium does not excrete cholesterol.

316.—Rothschild, M. A. Zur Physiologie des Cholesterinstoffwechsels. V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand. *Beitr. z. path. Anat. u. allg. Path.*, 60, 1914-15, 227-231. In fasting rabbits cholesterol is increased in blood, adrenals, liver and bile.

317.—Rothschild, M. A., and Rosenthal, M. The dietetic management of hypercholesterolemia in cases of cholelithiasis. *Amer. J. Med. Sci.*, 152, 1916, 394-403. "There is no synthesis of cholesterin in the body. Our supply of lipoids in maintained by our food intake." It has also been "demonstrated clinically that in experimental hypercholesterolemic states the blood shows a normal cholesterin content before the cholesterin content of the liver returns to normal." The bile is the only medium of cholesterol excretion. A series of cholelithiasis cases showed blood cholesterol of 0.122 — 0.425 per cent. It is suggested that gallstones are formed during periods of hypercholesterolemia, often as the result of a constitutional defect of cholesterol metabolism, but the blood cholesterol may be reduced by diets low in fat and cholesterol and by gall bladder drainage, etc.

318.—Rothschild, M. A., and Wilensky, A. O. Studies in Cholelithiasis *Amer. J. Med. Sci.*, 156, 1918, 239-247; 404-414; 564-574. I. The disturbances of the cholesterin metabolism as a factor in gallstone formation (239-247). II. The clinical relationship of the cholesterinemia to the pathological process. III. The immediate

effect of the various types of operations upon the cholesterinemia. The typical high blood cholesterol with cholelithiasis may be reduced by lipoid-poor diet, fever, or gall-bladder drainage.

219.—Rothschild, M. A., and Felsen, J. The cholesterol content of the blood in various hepatic conditions. *Arch. Int. Med.*, 24, 1919, 520-522. The blood cholesterol is elevated in proportion to the intensity of obstructive jaundice (250-700 mg. per 100 cc. blood). In other hepatic disorders blood cholesterol is not increased but usually reduced, and cholesterol is not proportionate to the amount of bile pigments in the blood. In hemolytic icterus (Banti's disease, pernicious anemia, chlorosis, leukemia, splenomegaly with icterus) there is no increase of cholesterol esters.

320.—Sagal, Z. Blood lipase in health and disease. *J. Med. Research*, 34, 1916, 231-240. Normal serum showed a slight power of splitting ethyl butyrate. Variations in different diseases were too slight for any diagnostic or prognostic significance.

321.—Sakai, S. Zur Pathogenese der Lipämie. *Biochem. Ztschr.*, 62, 1914, 387-445. Digestion lipemia does not occur in rabbits. After fat-rich diet, anemic and toxic lipemia is more regular, prompt and intense than after fat-poor diet. Every lipemia is accompanied by a corresponding increase of cholesterol, explained by its solubility in fat. The slightly diminished blood lipase or esterase is considered suggestive. Phlorizinized dogs show a slight lipemia.

322.—Savini, E. Sur les lipoides des leukocytes. *Arch. méd. belges*, 74, 1921, 325-329.

323.—Schenk, F. Kastration und Adrenalingehalt der Nebenieren. *Arch. exp. Path. u. Pharm.*, 64, 1911, 362-368.

324.—Schiller, H. Estimation of fats, cholesterol and sugar in the blood of thirty pregnant women. *Surg. Gynec. Obst.*, 29, 1919, 450-454. At various stages of pregnancy, also with obesity, albuminuria, etc., the author found normal sugar, fatty acids 0.285 — 0.570%, and cholesterol 0.163 — 0.415 in the blood. No parallelism was found between blood sugar and cholesterol.

325.—Schiffers, J. C. Bestimmung der Blutlipoide nach Bang. *Jahrbuch f. Kinderh*, 43, 1920, 151-159. The fat content of whole blood was found fairly constant in infants and older children, sick or well, except that in the exudative diathesis the values were only about half normal. Total cholesterol was the same in all the age groups. Among older children the cholesterol esters were about twice as high in the normal individuals as in those with exudative and other troubles. In general, the ester content increased with age.

326.—Schmidt, H. B. The clinical study of hypercholesterinemia. *Arch. int. Med.*, 13, 1914, 121-130 Cholesterol was found varying normally within narrow limits, but increased in obstructive jaundice, in six out of ten diabetics, and in most patients with arteriosclerosis, hypertension or nephritis.

327.—Schnable, T. G. Blood cholesterol in gastro-enterologic cases.

Amer. J. Med. Sci., 160, 1920, 423-428. Quoting the normal standards for blood cholesterol as set by Bacmeister and Havers at 110-180 mg., by Widal, Weill and Laudat at 174-195 mg., and by Bloor at 210 mg. in men and 230 mg. in women, the author accepts respectively 100 mg. and 200 mg. per 100 cc. as the lower and upper limits of normal. In two cases of carcinoma, the blood contained 120 and 180 mg. cholesterol per 100 cc.; in four catarrhal jaundice cases 144, 143, 214, and 171 mg. per 100 cc.; in one obstructive jaundice case 330 mg. per 100 cc. The figures in other diseases were variable. It was concluded that the blood cholesterol has little diagnostic value for gastroenterologic cases.

328.—Schulte, E. Zur Frage der Xanthelasmatischen Bildungen beim chronischen Ikterus. *Beitr. z. path. Anat. u. allg. Path.*, 61, 1915-16, 570-588. Description of one extreme case of xanthelasma, with discussion and literature.

329.—Scott, E. L. A lecithin-glucose preparation. Proc. Amer. Physiol. Soc., *Amer J. Physiol.*, 40, 1916, 145. "A preparation made by adding dextrose to emulsified lecithin and evaporating to dryness, exhibited some characteristics of a chemical compound; however, the dextrose could be separated by dialysis and if the lipoid was precipitated by colloidal Fe, the dextrose remained in solution".

330.—Segawa, M. Ueber die Fettarten der Niere mit besonderer Berücksichtigung des physiologischen und pathologischen Fettes. *Zieglers Beiträge*, 58, 1914, 1-47. By application of fat stains to 150 human kidneys, the author defines the character and distribution of lipoid substances in normal and pathological conditions. In acute nephritis neutral fat predominates and in chronic nephritis cholesterol esters.

331.—Seo, Y. Ueber das Vorkommen von Lipämie und über die Menge der Lipoidsubstanzen im Blut und Leber beim Pankreasdiabetes. *Arch. exp. Path. u. Pharm.*, 61, 1909, 1-6. Lipemia in totally depancreatized dogs is seldom sufficient to cause visible cloudiness of the plasma, but one case with milky serum is described. Analyses showed increase of ether extract of both plasma and corpuscles. Cholesterol and lecithin were correspondingly increased with the lipemia, but not in depancreatized dogs without lipemia. There was a great increase of lecithin, cholesterol and total ether extract in the liver.

332.—Sharpe, H. Two cases of cholesterin pleural effusion. *Brit. med. Jour.*, 1919 (2), 462-463.

333.—Siegfried, M., and Mark, H. Zur Kenntnis des Jecorins. *Ztschr. physiol. Chem.*, 46, 1905-6, 492-496. Analyses and discussion showing that jecorin is not a definite compound.

334.—Siemens. Ueber ungewöhnlich ausgebreitete Xanthomatose ohne Hypercholesterinämie. *Arch. f. Dermatol. u. Syphilis*, 138, 1922, 431-432. A case of remarkably generalized xanthomatosis, extending to the mucous membranes. The blood cholesterol was not increased. The etiology was therefore assumed to consist in increased local affinity for cholesterol.

335.—Simpson, Miriam E. The experimental production of macrophages in the circulating blood. *J. Med. Research*, 43, 1922, 77-144.

336.—Sisto, P. Ricerche sulla colesterinemia. Malattie del sangue e degli organi ematopoietici. *Gior. di. clin. Med.* (Parma), 1, 1920, 429-438.

337.—Sisto, P. Ricerche sulla colesterinemia. Malattie acute da infezione; tuberculosi polmonare. *Riv. ospedal.* (Roma), 10, 1920, 475-484.

338.—Sisto, P. Ricerche sulla colesterinemia. III. Malattie del fegato e delle vie biliari; diabete. *Riv. crit. di. clin. med.* (Firenze), 21, 1920, 409-414. The above studies agree with the findings of other authors. In particular, in 7 diabetic cases blood cholesterol was 0.191 — 0.590 per cent.

339.—Slemons, J. M., and Curtis, C. S. Cholesterol in the blood of mother and fetus; a preliminary note. *Amer. J. Obstet.*, 75, 1917, 569-575. The total lipoids of maternal blood at term were 600-1200 mg. per 100 cc., as against 500-700 mg. in fetal blood, the discrepancy indicating that the placenta is not permeable to fat. The free cholesterol of fetal blood was identical with that of maternal blood, but in deliveries without anesthesia esters were entirely absent from fetal blood, so that the total cholesterol was much less than in maternal blood. It is therefore concluded that the placenta is permeable to free cholesterol, but not to cholesterol esters.

340.—Slowtzoff, B. Ueber die Resorption des Lecithins aus dem Darmkanal. Hofmeisters Beiträge, 7, 1906, 508-513. Although lecithin can be saponified by the steapsin of the pancreatic juice, yet part of it is absorbed as such and can be demonstrated in the lymph.

341.—Small, J. C. The role of cholesterol in pathology. *J. Lab. and Clin. Med.*, 1, 1916, 785-803. Review of literature.

342.—Smith, Christianna. A study of the lipoid content of the kidney tubule. *Amer. J. Anat.*, 27, 1920, 69-93. Studying the kidneys of dogs, cats, rabbits, and rats with special stains, the author describes the distribution of fat and the differences between species.

343.—Smith, F. H., Wells, C. A., and Ewing, P. V. The changes in composition of butter fat produced by feeding cottonseed oil. *Georgia Agricultural Experiment Station*, Bull. 122, 1916, 95-111. (*Chemical Abstracts*, 10, 1916, 2773). Oil feeding decreased the saponification number and the content of water soluble fatty acids in butter and increased the content of insoluble acid. The constituents of the oil were not transferred to the butter fat in the same combinations or proportions in which they existed in the oil.

344.—Soper, W. B. Zur Physiologie des Cholesterinstoffwechsels. VI. Ueber Beziehungen der Milz zum Cholesterinstoffwechsel. *Beitr. z. path. Anat. u. allg. Path.*, 60, 1914-15, 323-244. Gradual moderate increase of blood cholesterol frequently results from extirpation of the spleen in rabbits, but not from mesothorium radiations of

the spleen. Hypercholesterolemia gives rise to cholesterol deposits in the reticuloendothelial cells of the spleen.

345.—Starkenstein, E. Ueber die Unabhängigkeit der Diastasewirkung von den Lipoiden. *Biochem. Ztschr.* 33, 1911, 423-435. Contrary to Lapidus, Bang and others, the author finds no influence of lipoids upon diastase activity.

346.—Starling, E. H. The significance of fats in the diet. *Brit. Med. J.*, 1918 (2), 105-107. A discussion from the standpoint of war diet, without experiments.

347.—Stepp, W. Experimentelle Untersuchung über die Bedeutung der Lipoide für die Ernährung. *Ztschr. f. Biol.*, 57, 1911, 135-170. Mice die on alcohol-ether extracted diets, and are not saved by the sole addition of butter, various neutral fats, or lecithin.

348.—Stepp, W. Ueber lipoidfreie Ernährung und ihre Beziehungen zu Beriberi und Skorbut. *Dtsch. med. Wchnschr.*, 40, 1914, 892-895. A further statement of the view that one or several unknown lipoids are necessary for life, in addition to known vitamines.

349.—Stepp, W. Die Lipoide als unentbehrliche Bestandteile der Nahrung. *Ztschr. f. Biol.*, 66, 1916, 365-386. Further experiments support the above conclusion. The essential lipoids must enter the body through the alimentary canal. Parenteral injection is ineffectual.

350.—Stepp, W. Ueber Versuche mit lipoidfreier Ernährung an Ratten und Hunden. *Ztschr. f. Biol.*, 69, 1919, 495-513. Life on lipoid-free diets is prolonged only for a few months by addition of vitamines.

351.—Stepp, W. Beobachtungen über den Cholesteringehalt des Blutes und der Galle bei lipoidfrei ernährten Tieren. *Ztschr. f. Biol.*, 69, 1919, 514-516. In the blood of three dogs on lipoid-free diets, in 2 instances subnormal cholesterol values were found (0.065—0.1%) but in 1 instance a somewhat elevated value (0.162%). In gall-bladder bile in 4 instances a subnormal cholesterol value was found (0.096, 0.03, 0.0755%).

352.—Stepp, W. Die Lipoide in ihrer Bedeutung als accessorische Nährstoffe. *Med. Klin.*, 16, 1920, 57-60.

353.—Stern, G. Ueber den Cholesterinspiegel im Blutserum Scharlachkranker. *Ztschr. f. Kinderh.*, 25, 1920, 129-133. There is first hypocholesterolemia in beginning of scarlatina, gradually rising to lower limit of normal, remaining there for entire 6 weeks' period of observation. In 1 case values were on lower limit of normal throughout. Theories of rôle of cholesterol in immunity, etc., are considered premature and unproved.

354.—Sternberg, H. Die Nebenniere bei physiologischer (Schwangerschaft) und artifizieller Hypercholesterinämie. *Beitr. z. path. Anat. u. allg. Path.*, 60, 1914-15, 91-115. The increase of lipoids in the adrenal cortex, with the cholesterolemia of pregnancy or cholesterol feeding, indicates a lipoid storing function.

355.—Stewart, M. J., and Forsyth, J. A. C. On the occurrence of massive cholesterin deposits in the breast in cases of long-standing

mastitis. *Brit. J. Surg.*, 8, 1920, 59-63. Cholesterol deposits and "foam" cells are described as a result of old inflammation and exudates in breast.

356.—Strathmann-Hollweg, H. Untersuchungen über den Cholesteringehalt des Blutserums. *Monatsschr. f. Kinderh.*, 19, 1920-21, 20-27.

357.—Strauss, H. Problems des Cholesterinstoffwechsels. *Med. Klin.*, 17, 1921, 20-22. Merely a small review of current literature.

358.—Terroine, E. F. Variations lipo-cholestérinémiques au cours de l'inanition et de l'alimentation. *J. de physiol. et de path. gén.*, 16, 1914, 386-97. Hyperlipemia does not alway occur in fasting. Blood cholesterol falls in the early part of inanition, then rises if there is lipemia, otherwise falls continuously toward end. Cholesterol decreases in the tissues. The feeding of 125 gm. pork or mutton fat caused increase of not only fatty acids but also cholesterol in blood.

359.—Thaysen, Th. E. H. Einige kritische Bemerkungen zur histiochemischen Grundlage der Cholesterinsteatose. *Centralbl. f. allg. Path. u. path. Anat.* 26, 1915, 433-451. (*Chemical Abstracts*, 10, 1916, 72). Results by any of the microchemical methods do not correspond to the results of direct analysis, and therefore the latter is the only reliable method for demonstrating the existence of cholesterol-steatosis.

360.—Tsunods, T., and Umehara, N. Weitere Mitteilung über vergleichende Studien der experimentellen Atherosklerose durch verschiedene Nahrungsmittel. *Verhandlungen der Japanischen pathologischen Gesellschaft*, 6, 1916, 90-93. Arteriosclerosis was produced in rabbits by feeding 6 to 10 months on a diet containing powdered brain. Various other substances caused or increased vascular lesions. Tallow, lard, or codliver oil caused only slight atherosclerosis in 12 to 18 months, and vegetable fat had still less effect. Arteriosclerosis was not produced in dogs by one or two years of admixture of brain powder with the diet, but with chronic P poisoning, arteriosclerosis was produced .

361.—Tsunoda, T., and Umehara, N. Beiträge zur Kenntnis der Lipoidose der Tiere. *Verhandl. d. jap. path. Gesellsch.* (Tokyo), 8, 1918, 216.

362.—Usuki, Die Fettverdauung im Magen und Dünndarm und ihre Beeinflussung durch Lecithin. *Arch. f. exper. Path. u. Pharm.*, 63, 1910, 270-93. With milk feeding, addition of lecithin or egg yolk accelerates emptying of the stomach and digestion of fat.

363.—Van Leersum, E. C. Zur Frage der experimentellen alimentären Atherosklerose. *Virchows Arch.*, 217, 1914, 452-462. Criticism and debate concerning pathological changes produced in rabbits by animal diet. Of 4 rabbits fed with egg yolks or cholesterol, only one showed doubful patch in aorta.

364.—Verse, M. Ueber die Blut-und Augenveränderungen bei experimenteller Cholesterinämie. *Münch med. Woch.*, 63, 1916, 1074-1076. Feeding rabbits with cholesterol in oil produces not only cholesterolemia, as discovered by Russian authors, but also lipemia. Within 5 weeks there is permanent opacity of the serum, also

emaciation and anemia. The cholesterol and oil mutually favor each other's absorption. All the changes are much less marked when either cholesterol or oils is fed alone. "Without cholesterol no lipemia". The cholesterol deposits in endothelium, liver, etc. are supposed to hinder egress of fat in experimental and diabetic lipemia.

365.—Voegtlin, C., and Bernheim, B. M. The rôle of the portal circulation of the liver in bile formation and jaundice. *J. Pharm. and Exp. Therap.*, 2, 1910-11, 455-467. The amount of bile formed by the liver depends upon the blood flow through it. The jaundice and fatal toxemia resulting from occlusion of the common bile duct are prevented by an Eck fistula. One dog in particular appeared able to live indefinitely in this condition.

366.—Wacker, L., and Hueck, W. Chemische und morphologische Untersuchungen über die Bedeutung des Cholesterins im Organismus. *Arch. exp. Path. u. Pharm.*, 71, 1912-13, 373-394. Good agreement of histological and chemical tests is claimed for cholesterol esters but not for free cholesterol. Free cholesterol is a stable component of cell structure, while cholesterol esters vary with different conditions such as diet. References are made to increase of cholesterol in adrenal cortex in pregnancy, arteriosclerosis, diabetes, chronic heart disease, nephritis and liver cirrhosis, and reduced content in sepsis, chronic tuberculosis and cancer.

367.—Wacker, L., and Hueck., W. Chemische und morphologische Untersuchungen über die Bedeutung des Cholesterins im Organismus. *Arch. exp. Path. u. Pharm.*, 74, 1913, 416-441; 442-449; 450-460. The plasma contains both free and combined cholesterol, while the red cells contain only the free form and no esters. The red corpuscles of horse blood yield 0.360 percent free cholesterol, and the leukocytes 1.729% free and 0.04% esterized cholesterol. Cholesterol feeding increases not only cholesterol but also other lipoids in the blood. Slight increase of blood cholesterol is accompanied by much greater enrichment of the organs with cholesterol.

368.—Warner, D. E., and Edmond, D. H. Blood fat in fowls. *J. Biol. Chem.*, 34, 1918, 171-174. Dispute with Riddle and Harris.

370.—Weems, B. F. Jr. Cholesterohydrothorax. Observations upon a case. *Amer. J. Med. Sci.*, 156, 1918, 20-30. After pleurisy dating back to 1907, aspiration in 1916 yielded fluid glistening with cholesterol crystals. The whole blood contained 2.5 mg. and the serum 3 mg. per cc. The urine was free from cholesterol.

371.—Weltmann, O., and Biach, P. Zur Frage der experimentellen Cholesteatose. *Ztschr. exper. Path. u. Therap.*, 14, 1913, 367-378. Carnivora have efficient liver function for disposing of cholesterol through the bile. Cholesterol feeding of herbivora causes increase of blood cholesterol and also accumulation in the liver, chiefly in combined form. Uranium poisoning of hypercholesterolemic animals results in anisotropic deposits in the degenerated cells.

372.—Widal, F., Weil, A., and Laudat, M. La lipemie des brightiques;

rapports de la rétinite des brightiques avec l'azotémie et la cholestérinémia. *Semaine Méd.*, 32, 1912, 529-531. Marked lipemia (over 3% blood fat and over 1% cholesterol) was found in nephritic cases with and without retinitis. Low lipoid figures were also found in various cases. Every lactescent serum is lipemic but not every lipemic serum is lactescent. It is considered impossible to isolate a lipemic syndrome in nephritis. Retinitis is not due to hypercholesterolemia, for it occurs with and without high blood lipoids; also the preliminary lesion is a fibrinous exudate and the lipoid deposits are secondary.

373.—Windaus, A. Ueber die quantitative Bestimmung des Cholesterins und der Cholesterinester in einigen normalen und pathologischen Nieren. *Ztschr. physiol. Chem.*, 65, 1910, 110-117. A slight increase of free cholesterol and a great increase of cholesterol esters are found in amyloid kidneys as compared with the normal.

374.—Wohlgemuth, J. Ueber das Labferment. *Biochem. Ztschr.*, 2, 1907, 350-356. Hemolysin is activated by lecithin to form a toxolecithid.

375.—Wohlgemuth. J. Untersuchungen über den Pankeassaft des Menschen. IV. Ueber ein in ihm enthaltenes komplexes Hämolysin und über die Darstellung des Lecithids. The hemolytic power of pancreatic juice can be activated by lecilhin.

376.—Yoshimoto. S. Ueber den Einfluss des Lecithins auf den Stoffwechsel. *Ztschr. physiol. Chem.*, 64, 1910, 464-478. Lecithin feeding results in retention of both nitrogen and phosphorus.

377.—Zucker, T. F. Studies in the absorption of fats. *Proc. Soc. Exp. Biol. and Med.*, 17, 1919-20, 89-91. Using Bloor's method, no excess of fatty acids, phosphatids or cholesterol was found in the portal blood as compared with the jugular blood of a 14 kg. dog during digestion of 50 gm. olive oil. Any absorption through the blood must therefore be too small for detection by existing methods.

3.1

STUDIES IN ARTHRITIS: THE BLOOD GASES AND BLOOD FLOW.* † ‡

By

By RALPH PEMBERTON, M. D.; BYRON M. HENDRIX, Ph. D., and CAROLINE Y. CROUTER, M. S.

From the Presbyterian Hospital, Philadelphia, Pa.

The provision during the war for the intensive study and treatment of arthritis was productive of clinical and laboratory data on a scale which had not hitherto been presented under controlled conditions. The publications of these data[1] were followed by another contribution[2] in which the attempt was made to interpret them with the aim of formulating a tentative hypothesis on the general nature of arthritis. The present contribution reports the attempt to test the validity of such an hypothesis and to contribute further data bearing on the subject of arthritis.

In the foregoing army studies an opportunity for further investigation was afforded by the so-called glucose tolerance test. This revealed a lowered sugar tolerance in a significant percentage of cases of arthritis, which returns, or tends to return, to normal with recovery or convalescence. To a large degree this parallels the incidence of focal infection. Without attaching too much importance to a lowered sugar tolerance *per se*, it was taken as an index of some of the disturbed physiology causing the arthritic symptoms and was studied with the aim of ascertaining some of the determining factors concerned. It was believed that in the presence of this lowered

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† The expenses of this investigation were defrayed by contribution from several sources including a number of patients. Obligation should be expressed to Mr. E. K. Swigart of Milwaukee, and particularly to the late Mr. John H. McFadden of Philadelphia, whose interest in chemical research was expressed in many directions by broad minded generosity.

‡ The work here recorded is part of a study on Arthritis in collaboration with Robert B. Osgood, M.D. of Boston.

tolerance there might be detected other disturbances possibly too subtle to yield measurable contrasts in cases not presenting it.

The hypothesis above mentioned involved the conception that arthritis is referable in part to interference with some phases of oxidative metabolism, either systemically, or locally, or both. In this connection, it may be mentioned that 20% of the cases studied among soldiers presented a basal metabolism slightly below normal.

It was determined therefore to investigate, as a starting point, the gaseous equilibrium of the circulating blood during the conduction of a glucose tolerance test in those cases which gave a lowered tolerance. A series of 21 tests was conducted in the following manner: After a fast of about fifteen hours, 6 P.M. to 9 A.M., a sample of venous blood was taken under oil from the median basilic vein and the patient was given 100 gm. of glucose (C.P.) in 150 cc. of water. A second sample of blood was taken a half hour after, and the third one hour after the ingestion of glucose. The patient was kept at rest during the test and the amount of blood sugar was immediately determined by Maclean's titration method.[3] The Maclean titration method for blood sugar was used in preference to the Benedict modification of the Lewis Benedict method, utilized in the previous studies, because of the more dependable figures obtained.

The results from this method were in concordance with those previously published for arthritics, although the figures were somewhat lower and the percentage incidence of a lowered sugar tolerance in arthritis was possibly slightly less. This small difference, however, must be correlated with the differing natures of the groups studied.

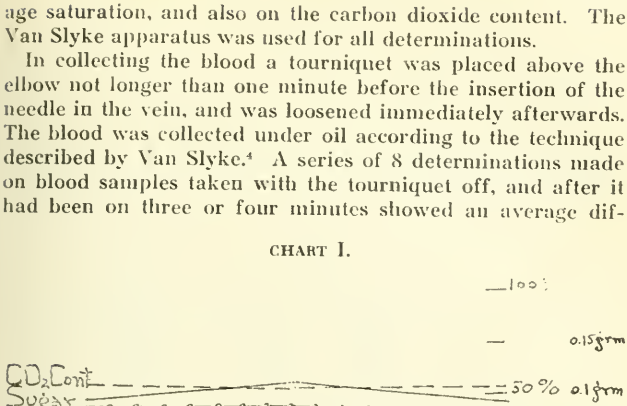
Of 21 cases of arthritis studied, 13 or 61 percent gave an abnormally low sugar tolerance, namely, the blood sugar was above 150 mg. per 100 cc. of blood or was still at that point an hour after the glucose was taken. The average high point was .173 percent but many cases gave much higher figures. The chart shows this graphically.

Coincidently with observations on the blood sugar, determinations were conducted on the oxygen content and the oxygen capacity of the blood in order to determine the percent-

age saturation, and also on the carbon dioxide content. The Van Slyke apparatus was used for all determinations.

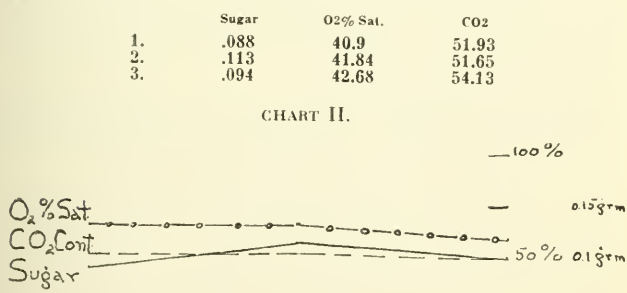
In collecting the blood a tourniquet was placed above the elbow not longer than one minute before the insertion of the needle in the vein, and was loosened immediately afterwards. The blood was collected under oil according to the technique described by Van Slyke.[4] A series of 8 determinations made on blood samples taken with the tourniquet off, and after it had been on three or four minutes showed an average dif-

CHART I.



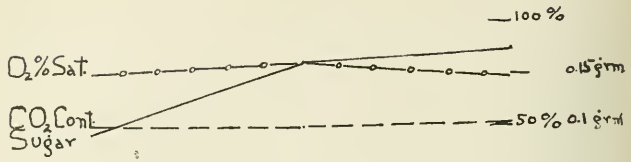
	Sugar	O2% Sat.	CO2
1.	.088	40.9	51.93
2.	.113	41.84	51.65
3.	.094	42.68	54.13

CHART II.



	Sugar	O2% Sat.	CO2
1.	.086	64.04	49.54
2.	.112	65.91	50.33
3.	.102	61.54	50.61

CHART III.



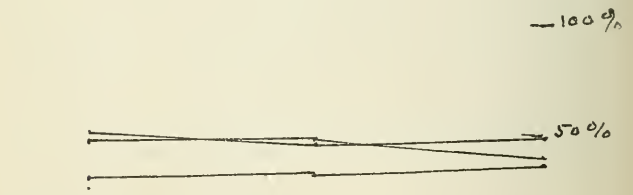
Arthritics - Low Sugar Tolerance.

	Sugar	02% Sat.	CO2
1.	.091	76.33	51.65
2.	.163	82.44	50.38
3.	.175	76.31	51.24

ference between the two samples of only 1.25 cc. of oxygen per 100 cc. of blood. This gives a maximum variation in the per cent saturation of 5-7%. It was decided that any difference produced by keeping the tourniquet on less than a minute would be within the limits of experimental error. Further observations conducted subsequently showed that the effect of a tourniquet is to increase the percentage saturation rather than to lower it.

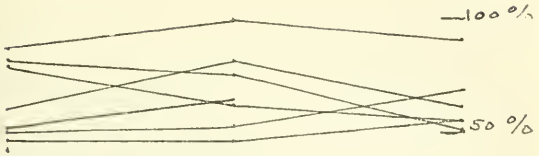
After the ingestion of glucose the CO_2 content remained practically unchanged but the oxygen percentage saturation rose in the majority of instances. (See Charts 1 to 6 inclusive).

CHART IV.



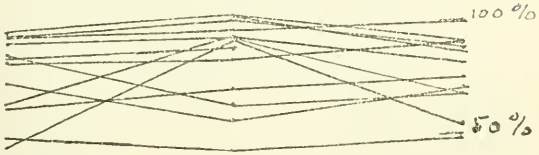
Normals. O_2 % Sat.

CHART V.



Arthritics - Normal Sugar Tolerance. O_2 % Sat.

CHART VI.



Arthritics - Low Sugar Tolerance. O_2 % Sat.

Of the 13 arthritis cases showing a low sugar tolerance eleven showed a marked increase in the oxygen percentage saturation, whereas of the eight arthritic cases showing a normal sugar tolerance, only three showed an increase in the oxygen percentage saturation.

The average of all oxygen percentage points

in the 13 arthritic cases that gave a low sugar tolerance was 78.37%
in the 8 arthritic cases with normal sugar tolerante was 64.06%
in 3 normal persons giving a normal sugar tolerance was 41.81%.

There is in this a suggestion that some of the pathology reflected by a lowered sugar tolerance may be detected in a more delicate way by study of the percentage saturation of oxygen, though further data are needed before this could be

postulated in all cases.

The average oxygen percentage saturation at fasting level was as follows:

For the 13 arthritic cases with low sugar tolerance 76.33%
For the 8 arthritics with normal sugar tolerance... 64.04%
For the 3 normal persons with normal sugar tolerance 40.90%.

The oxygen percentage saturation was determined under fasting conditions in a total of more than 100 individuals of whom 77 were arthritics. In general, the average oxygen percentage saturation for arthritics under the conditions of observation ran slightly though definitely higher than for normals and for other types of disease.

The following table gives figures for a variety of normal and diseased subjects under fasting conditions.

Oxygen percentage saturation of 77 arthritics	53.68%
" 12 normals	41.71%
" 7 nephritics	38.63%
" 2 diabetics	42.53%
Post lethargic encephalitis	39.03%
Tuberculosis	50.19%
Anemia pernicious	84.28%
" aplastic	68.66%
Pneumonia (convalescent)	77.84%
Typhoid	49.60%
Asthma	43.67%

42.3 % of arthritics gave a saturation above the average value of 54 %. The range in saturation for the normals here studied was from 27 to 51 %. The range in saturation for arthritics was from 26 to 97 %.

It is to be noted that cases of pernicious anemia show higher figures and the nephritics lower figures. It is also of interest to note that the highest figures, other than for arthritis, were in conditions in which the respiratory functions of the blood were supposedly disturbed in a mechanical or other manner.

It was a matter of some surprise that the diverse types of conditions studied did not show any large degree of disturbance in the same direction. It can hardly be believed that a disturbance of this nature can be concerned in such a small percentage of various disease conditions, and observations should be extended to include other such. Those cited suffice to indicate that these findings are not of general occurrence and that they are present in arthritis to an extent needing

explanation. The types of arthritis studied in the present series of seventy-seven cases presented nearly all phases of the disease and its sequelae, though a number of these cases had been previously studied elsewhere and subjected to treatment such as the removal of foci of infection. As a class they probably represented greater chronicity but no greater intensity than the cases studied among soldiers, though the worst types usually exceeded in complications and sequelae the worst types encountered among the soldiers. Brief mention will be made as individual cases are cited of the peculiarities of each.

In studying the blood gases it was obvious that factors which might influence them, such as anemia, fever, inanition and the like must be considered. An attempt to correlate such factors with the findings mentioned was unsuccessful. The following table gives the averages of the red cell counts for the several groups.

	average % saturation	average R. B. C.
Arthritics with high % sat (14) . . .	80.39	4,303,000
Arthritics with low % sat (11) . . .	43.51	4,289,000
Diffuse types of disease (4) . . .	50.3	3,387,000
Pernicious anemia	84.28	1,630,000
Aplastic anemia.	68.66	1,540,000

The following table contrasts certain degrees of robustness and anemia in the same connection.

	% Sat.	average R. B. C.
Mr. Baldwin, large, robust and very muscular	87.73	4,820,000
Mrs. Geyer, chair ridden but of fair nutrition	67.12	4,380,000
Miss Botts, chair ridden, of fair nutrition .	78.87	3,820,000
Miss Chapin, active and well nourished . .	79.77	4,100,000
Mr. Taylor, well nourished, well muscled and mildly active	82.91	4,980,000

Meakins[5] has hown that subjection of a part to extreme cold or heat may cause the oxygen percentage saturation of the venous blood in it to vary between very wide extremes, and Barcroft & Nagahaski[6] have corroborated this. The influence of minor changes of temperature is doubtless in the same directions respectively, and we have endeavored to explain our findings on such a basis. The figures for normals and arthritics, however, were obtained under apparently average and often identical condi-

tions. The difference between the groups is also reflected during the performance of the sugar tolerance tests. Again, some cases have been followed for over a year and have consistently given figures at or about the same levels, irrespective of the season or place of observation, whether hospital room or ward, hotel room or laboratory. The changes in external temperature for some such cases have varied from the heat of Philadelphia summer to the cold of winter with intermediary observations in spring and fall. Several arthritics who gave low figures maintained essentially low figures throughout, and several with high figures maintained these.

The following are illustrative:

Cases with figures fairly consistently at higher levels.

Case 1 Miss Botts		Case 3 Miss Chapin	
11/10/20	78.87%	11/29/30	79.77%
2/ 3/21	69.41	2/26/21	60.04
5/ 4/21	74.14	4/18/21	82.97
5/18/21	76.36	5/13/21	85.68
6/24/21	68.13	9/26/21	79.22
		11/16/21	88.75
Case 2 Mrs. Geyer			
4/25/21	67.12	**Case 4 Miss Anthony**	
6/10/21	65.19	12/ 9/20	86.36
7/20/21	65.38	4/ 1/21	92.48
9/23/21	83.93		

Cases with figures fairly consistently at lower levels.

Case 5 Mrs. Branch		Case 7 Miss Folmer	
3/17/21	27.05	2/19/21	47.64
9/27/21	45.38	3/11/21	31.62
		5/11/21	33.77
Case 6 H. Zeresky			
9/19/21	52.05%		
9/27/21	34.46		
11/18/21	29.54		
12/ 5/21	29.96		
12/19/21	31.47		
12/16/21	30.09		

It is interesting to note, however, that coincident with improvement, especially that following removal of the apparent cause of the arthritis, the high oxygen percentage saturation when present sometimes fell. The number of instances in which this has been observed is as yet too small to justify

broad conclusions but the figures suggest that this may be a concomitant modification in some cases. The following table shows a fall coincident with improvement in six cases studied. In two others (cases 2 and 3 above) there was a rise or no marked change. It is probable that in interpreting such results one should be guided by the general condition of the patient and by the trend of the figures when several observations are available. There must be varying factors in the economy which at certain isolated times modify the gaseous equilibrium and conditions making for improvement, and some range of variation must be allowed for.

Case 1 Miss Cowling		Case 4 B. Lewis	
2/21/21	89.86	17/19/21	55.40
5/17/21	54.3	7/26/21	63.03
		9/20/21	35.57
Case 2 Mrs. Bell		9/26/21	34.26
12/20/20	80.00 (approximate)	Case 5 Mrs. Skill	
5/16/21	64.28	11/ 8/29	91.96
		3/10/20	57.94
Case 3 Miss Lathrop			
1/14/21	93.81	Case 6 Taylor	
6/ 2/21	36.36	12/31/20	82.91
		5/20/21	39.36

Some of these cases justify brief mention because they illustrate improvement after a variety of measures.

Case 2, Mrs. Bell, presented arthritis of both knees and at the time of the second determination was free from all subjective or objective symptoms. This condition followed a course of hydrotherapy and medication and later confinement to a wheel chair after having had her knees straightened and placed in casts. Case 3, Miss Lathrop, presented a widespread and chronic arthritis with much deformity due apparently to pansinusitis. At the time of the second determination she was essentially free from discomfort a few weeks following a successful sinus operation. Two days later, however, she developed bilateral phlebitis of the legs from which a fatal septicemia finally resulted and there was a very slight rise in the figures on the date mentioned. Case 1, Miss Cowling, presented widespread chronic involvement of many joints. On the date of the second determination she had made a very substantial improvement in her systemic as well as her arthritic

condition, following removal of dental foci and broad tonic treatment with arsenic, the iodides, etc. Mrs. Skill, case 5, presented widespread chronic involvement and on the date of the second determination was feeling very greatly improved under a regime of hydrotherapy and associated medication along orthodox lines. Case 6, Taylor, presented late convalescent stages of a chronic arthritis originating in the army during the war. The second determination was made when he had experienced further benefit referable apparently to treatment of pyorrhea and associated orthodox medication. Case 7, Miss Follmer, presented arthritis of several years' duration in knees and hips. The second observation was made after the removal of several dental foci which was followed by a moderate degree of improvement.

A study of the factors having a favorable or unfavorable influence upon the arthritic processes was of some interest. Food, exercise, drugs, etc., were found to play an important role. The effect of food can be readily observed by comparing the average of all % saturation points determined during the glucose tolerance test with the average of the determination made on fasting blood. The percentage saturation rose with few exceptions after the ingestion of glucose, reaching the highest values, as a rule, in the cases showing a lowered sugar tolerance. This was often apparent, even at the moment of obtaining the blood, from the fact that the second and third blood samples were generally much brighter in color than the first, indicating a higher oxygen content. The action of drugs is less definite. Studies on the percentage saturation of oxygen before and after the administration of fifteen grains of aspirin were made in eleven cases, five of which were fasting. In three of these it showed a slight rise, in six of them a fall, and in two remained virtually unchanged.

	Percent rise or fall		effect felt
Zaresky fasting	+	11%	less pain
Lewis fasting	+	7%	more limber
Huquenle non fasting	+	7%	?
Cassidy " "	—	8%	?
Geyer fasting	—	7%	?
Merideth fasting	—	16%	less pain, greater motion in hands
Pierce non fasting	—	26%	less pain
Farrell non fasting	—	2%	less pain
Folmer non fasting	—	12%	less pain, more limber
Wiggins fasting unchanged			none
Roop non fasting "			none

In an effort to determine whether the mechanism causing the high saturation was due to vaso-constriction and, further, to the influence of high blood pressure, the effect of adrenalin was studied in one case. The patient was an ambulant asthmatic who was receiving fairly frequently 1 cc. of a 1 to 1000 solution of adrenalin chloride. As the accompanying table shows:

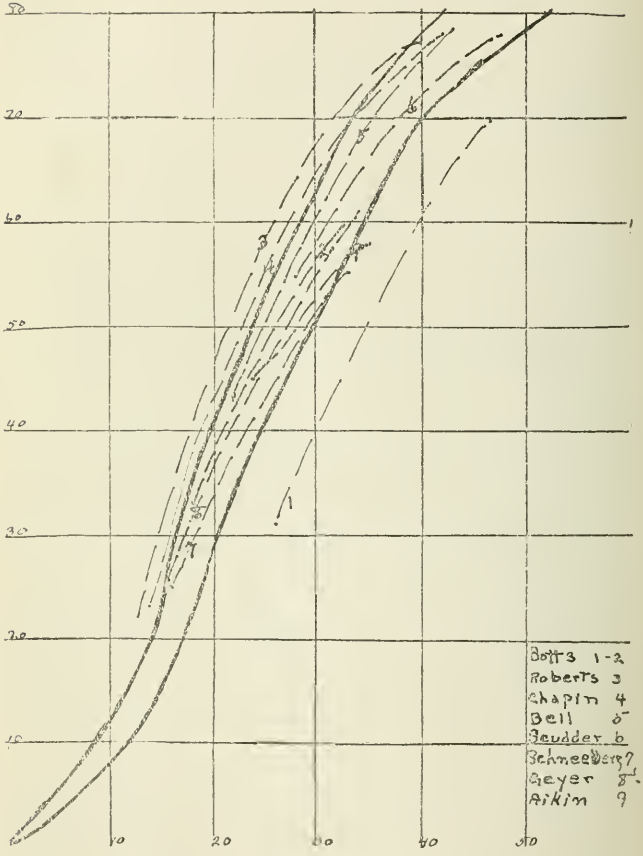
	Before	After
% sat.	43.67 %	38.2 %
B. P.	60-48	108-57
Pulse	68	72

the percentage saturation fell while the blood pressure increased markedly from 60 systolic and 48 diastolic to 108 systolic and 58 diastolic.

Studies of the percentage saturation of the arterial blood in these several connections would be of value and are in progress.

In undertaking the studies here recorded it was planned to include a study of the dissociation curves of blood for oxygen and carbon dioxide along the lines developed by Barcroft, Haldane and others. The oxygen dissociation curves of twelve arthritics and one normal were determined according to the method of Barcroft[7]. Samples of blood were exposed to two pressures of O_2 (40 and 20 mm.) in the presence of 40 mm. pressure of CO_2 (approximately that of the aveolar air) and the amount of O_2 taken up by the blood under given conditions was determined by Van Slyke analysis. Two 200 cc. tonometers were exhausted by means of a suction pump, filled with the desired gas mixture from the supply tank, exhausted and filled again. The amount of CO_2 calculated to give 40 mm. preassure was then forced into the tonometers from a CO_2 burette. Four to five cc. of blood were drawn into a pipette, the end of this was joined to the tip of one tonometer by a short piece of rubber tubing, and the blood with the exception of the first and last drops was forced into the tonometer. When both tonometers had been so filled, they were rotated in a horizontal position in a large tank filled with water at 37°-37.5° C. After five minutes, the stop cocks were opened (under water) to reduce the excess pressure. After ten minutes the tonometers were released and held per-

CHART VII



pendicularly under the water until the blood drained into the lower and narrow end. Hot water was then poured over the top of them in order to increase the pressure sufficiently to force out the blood. The first few drops of blood were wiped

off from the tip of the tonometer which was then connected to the tip of a 1 cc. pipette by means of a small piece of tubing. The blood flowed rapidly into the pipette and was then measured directly into a Van Slyke apparatus so that contact with the air was practically negligible. Samples of gas from the tonometers were drawn off into a Haldane apparatus and the CO_2 and O_2 were determined in the usual way. Experiments were carried on in duplicate in most cases.

The curves fell within essentially normal limits. One fell below normal because the alkali reserve of the blood, as indicated by the CO_2 content was definitely lower than normal. The patient had been on a restricted diet for six months and showed marked improvement. Two fell slightly above, for reasons that are not entirely understood.

In interpreting these results certain considerations must be borne in mind. The circulating systemic blood from a large vein of the forearm was used. It is needless to point out that if the blood could have been examined when in closer contiguity to the affected regions other results might have been obtained, as the tendency of the blood as a whole to maintain its equilibrium is well recognized. Local interference with oxidative relations, from whatever cause, would presumably be followed by local chemical changes not necessarily reflected in the systemic blood. Study of the gases and dissociation curves of the blood coming immediately from an affected joint would be of much interest.

"Blood Flow"

In view of the evidences of change in the percentage saturation of the oxygen of the venous blood in arthritis under the conditions described, and the difficulty of explaining this upon a chemical basis through study of the dissociation curves, attention was directed toward the possibility of changes in the vascular system as a factor to this end. It has been shown (H. G. Wells[8]) that the blood coming through an inflamed area is characterized by a lower content of CO_2 and a higher content of oxygen, due for the most part to the increased blood flow accompanying hyperemia. This is doubtless partly true in a systemic sense after a "bake" of the whole body and one observation conducted by the present

writers upon the blood flow, during an electric bake of the whole body, also suggests such an explanation. The attempt was therefore made to correlate cases showing a high percentage saturation of oxygen in the venous blood, with an increased blood flow in the limb examined.

Studies were conducted on the rate of blood flow through the hand in seventeen arthritics and six normals by means of the calorimetric method of Stewart.[9] Calorimeters were constructed on lines similar to those used by him and gave satisfactory results.

A tin lined copper vessel of 3700 cc. capacity with a flanged opening in the top just large enough to permit the passage of a hand, was placed inside a 14 inch deep metal container of 10 inch diameter. A layer of cork chip was packed all about the copper vessel and an additional inch thick slab of cork was fitted into the top of the outer vessel and around the flanged opening, to insure the least possible conduction of heat. Three small openings were cut through the cork and the top of the outer vessel; one for a thermometer and two for quills used to stir the water during a determination. The loss of heat per minute when the calorimeter was filled with water at about 30 degrees C. was determined and the necessary corrections were made for this loss in the subsequent work on rate of flow. The water equivalent of the calorimeter was also determined. The hand volume was found by plunging the hand up to a mark at the head of the ulna, into a can of water filled to overflowing; the can was weighed before and after displacement of the water, and the loss of weight in grams. was taken as the volume of the hand in cubic centimeters.

In carrying out a determination, the patient sat first for ten minutes with his hands in a tank of water at about 30° C. The hands were then quickly dried off, strips of felt were placed about the wrists just above the head of the ulna and the hands were plunged at once into the calorimeters so placed that the arms could hang down in a natural position. The calorimeters were previously filled with about three liters of water from the large tank and weighed. The felt filled the opening around the wrists but was not packed in so tightly as to interfere with the circulation. The temperature of the water in each calorimeter was read once a minute for ten minutes, care being

taken to stir the water thoroughly before each reading. The patient was told not to move his hands, but to let them hang loosely with fingers spread apart.

From the amount of heat taken up by water in ten minutes the amount of blood which must necessarily pass through the hand in that time to supply that heat was calculated by Stewart's formula.

$$Q = \frac{H}{T-t} \times \frac{1}{S}, \text{ i. e.:}$$

quantity of blood flowing thru hand=

$$\frac{\text{Heat taken up by calorimeter}}{\text{arterial temp.—venous temp.}} \times \frac{1}{\text{specific heat of blood}}$$

The arterial temperature was assumed to be that of the mouth and the mean of the temperature of the water at the beginning and close of the experiment was taken as the venous temperature.

Since there is wide variation in the size of different hands, it would be obviously unfair to compare the absolute rate of flow in cc. per minute of a large hand with that of a small hand and the rate is therefore expressed in terms of the number cc. per minute per 100 cc. of hand.

It was found that such factors as food, exercise, position, etc., had a marked effect on the rate of flow and care was taken to carry on experiments under conditions as nearly identical as possible. Determinations made when the patient was fasting and again after fasting showed the following contrast:

Rate of Blood Flow in cc. per minute per 100 cc. of hand.

			Left	Right	Average
Normals	Fasting	(6)	9.1	9.1	9.5
	Non Fasting	(4)	11.5	10.6	11.1
Arthritics	Fasting	(6)	8.4	8.2	8.3
	Non Fasting	(17)	10.7	11.3	11.0

A series of determinations under increasing degrees of bodily activity was carried out on two arthritic patients and showed the following effect of food and exercise in increasing the rate of flow:

Time	Position	Blood Flow	% Sat.
Lewis			
9. A. M.:	Just awake, fasting lying in bed with arm hanging over edge . .	1.3	55.40
12. M.	Fasting, has been walking about Sat for experiment	3.1	
12.45	Dinner; rested afterward. Sitting .	8.1	
	Walking to Lab. Sitting	8.3	
Lewis			
10. A. M.:	Fasting-Sitting.	8.5	63.03
10.40 A. M.:	Took 100 g. glucose in 200 cc. water.		
11.30	Sitting	12.7	69.75

This patient was rather spare and presented a severe spondylitis acquired in the army.

Farrell			
9.50 A. M.:	Not out of bed, arm hanging over edge.	8.5	
12.30	Had been up and about for an hour Sitting	16.5	
1.00	Dinner		
3.05	Walked to Lab. from ward. Sitting	17.4	

This patient was very well nourished and had chronic involvement of both knees.

The following table gives the figures under fasting conditions, for the rate of blood flow, percentage saturation of the blood with oxygen and the blood pressure in a series of normals, arthritics and patients with other diseases.

Normal Fasting	Rate of Blood flow in cc. per minute per 100 cc. of hand.	Oxygen per cent. saturation of venous blood.	Blood Pressure
Maxwell*	13.4	47.46	
B. M. H.	7.	50.56	
C. Y. C.*	5.9	33.71	
Brown*	8.75	37.73	
Arthritics Fasting			
Baldwin		87.73	165–100
Lewis	8.5	63.03	85–55
Lewis	1.3	55.4	
Geyer	5.95	65.38	115–72
Shemeld	6.2	46.64	100–60
Wallace	9.35	63.50	175–95
Farrell	11.85	66.98	105–85
Oller	7.7	39.92	110–65
Botts*	9.5	68.13	99–74
Zacharias*	9.0	50.14	130–85
Clarkson*	9.6	37.36	
Scudder*	6.45	37.15	130–80
Cowling*	15.5	54.3	
Nickell*	8.9	55.88	100–75
Ivancovitch	5.3	45.17	115–75
Diffuse Diseases			
Convalescent Pneumonia			
Clayton	10.8	77.84	95–50
Aplastic anemia			
Gormley	13.4	68.66	115–60

* Percentage saturation not determined on same day as rate of blood flow. The blood pressure values were not obtained immediately coincident with the percentage saturation or rate of blood but reflected the average pressure of the patient concerned.

In order to avoid differences referable to physical activity of any kind, thirteen determinations were made on eleven arthritics as soon as possible after waking in the morning. In all cases no food or water had been taken since the previous night, and, with only one or two exceptions, the patient had not moved out of bed or even sat up in bed. The average for the arthritics was 2.99 cc. per minute per 100 cc. of hand. Eight determinations on six normals, carried on under similar conditions, in fact on the same days as eight of the arthritics, gave an average of 3.06 cc. per min. per 100 cc. hand. The arthritics varied from 0 to 8.06 the normals from 2.1 to 4.8.

ARTHRITIS		NORMAL	
Chapin	8.06	Kennedy	3.03
Geyer	0.	Cunningham	3.90
Geyer	3.9	"	2.5
Beebe	2.50	G. Crouter	2.7
Wiggins	1.1	Hoy	2.1
Tull	1.8	"	3.1
Cowling	0.	Penner	2.1
Lewis	1.1	Mazzy	4.8
Lewis	0.9	Average	3.03
Branch	.95		
Branch	1.2		
Pollard	7.7		
Zaresky	2.6		
Average	2.44		

It is interesting to note that all figures taken before rising were much lower than any figures obtained later in the day and that differences between normals and arthritics were apparently more evident at that time. A more striking difference exists between similar determinations made during the summer and those repeated on the same individuals under the same conditions, on cold Fall days:

	Summer	Fall
Lewis	1.5	.9
Farrell	9.95	5.2
Geyer	5.7	3.9

Inspection of the above tables makes it difficult to detect any clear-cut or constant relation based on them between the blood flow of arthritics and that of normals or between the rate of blood flow and the oxygen percentage saturation of the blood. It will be seen that the rate of blood flow in the fasting

arthritics before rising, reaches considerably lower values than it does in the fasting normals under the same conditions although on the other hand there are also a few higher values.

The impression is gained, however, from the tables that the rate of blood flow in the arthritic varies more and may at times be considerably below normal. This is not reflected in the averages and may be merely a function of the asthenic stage in general. The rate of blood flow as shown by these results apparently does not account for the increased amount of oxygen in the venous blood, for it would seem that if the rate of blood flow were the cause of the increased percentage saturation in the venous blood, it would be greater than the rate of flow in normal individuals. The question is still under investigation, however.

In the effort to analyze the various factors which might contribute to a high percentage saturation or a change in rate of blood flow the blood pressure was also studied, but as shown in the table it seems to bear no discoverable relation to them.

Influence of "Bakes"

The influence on the human body of raising the external temperature has been studied to a limited degree and from a number of angles as regards normal physiology but has not been investigated in any large way as regards arthritis, although this perhaps is the condition in which such measures have their widest application. In a recent contribution[10] Haggard has shown that the rise in body temperature from exposure to a hot bath (43°C.) for 20 minutes produces a fall of alveolar CO_2 tension and of the CO_2 in solution in the blood. No compensatory changes in the CO_2 combining power of the blood occurred and the alkali in use was not lowered in proportion to the decrease in dissolved CO_2 . It was therefore deduced that the C_h is presumably lowered. Bazett and Haldane[11] observed a rapid rise in temperature and a fall in alveolar CO_2 accompanying hyperemia during prolonged sitting in a bath kept just above body temperature. The baths of Bazett and Haldane and of Haggard were hot water baths sometimes over much longer periods and had a more profound effect upon the body temperature than did the "electric bakes" shortly to be mentioned.

The rôle of carbon dioxide in arthritis has never been fully investigated but the known facts relating to its elimination through the sweat to a small degree normally, and to a large degree after a certain critical external temperature is reached, are significant in view of the wide clinical application of heat in arthritis and other factors. According to Starling[12] "at a temperature of 29° to 33°C. the CO_2 output by the skin is about 0.35 gm. per hour, i.e. about 8.4 gm. in the twenty four hours. When the external temperature rises above 33°C. the CO_2 output increases, so that at 34° it is doubled and at 38.5° it may amount to as much as 1.2 gm. per hour (Shierbeck). It is just at this temperature of 33°C. that a secretion of sweat begins to be noticeable, and it has been suggested that the increased CO_2 output may be due directly to the increased work and metabolism of the sweat-glands during their activity."

A series of determinations were therefore conducted, in the course of seventeen electric bakes on arthritics and normals, on the oxygen content and capacity of the blood; the CO_2 content and capacity of the blood; the aveolar CO_2; the body temperature; the bake temperature and in some cases the hemoglobin and corpuscular elements of the blood.

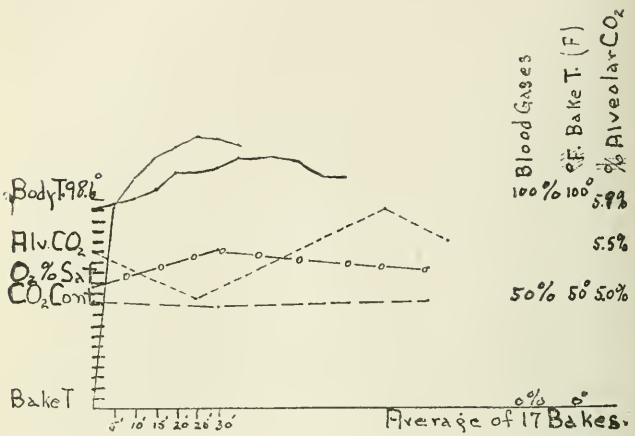
The "bake" was administered with an electric baker of the usual portable variety and continued for 20 minutes after the temperature under the hood reached 120°. A specimen of blood was taken before the bake, a second during or immediately after the bake, and a third from half an hour to an hour after the bake; in general after the body temperature returned to normal.

The temperature of the bake and the body temperature of the patient were taken every five minutes. An ordinary cooking thermometer fastened to a long stick was placed in a uniform position between the blanket and sheet covering the patient and could thus be quickly withdrawn and read.

Determinations were made of the alveolar CO_2 with the Fridericia apparatus before the bake and at varying intervals during and after the bake.

In 14 of the 17 cases, or 82%, the per cent. oxygen saturation rose owing, in 11 of the 14, to a marked rise in the O_2 content. The O_2 capacity either rose or fell slightly. As a rule the CO_2 content of the blood samples taken immediately at the close of the bake was lower than the initial CO_2 content, while

CHART VIII.



NOTE: The curve for alveolar carbon dioxide is diagrammatic as the average curve does not reflect the trend of the curve in most cases.

the majority of the final analyses about a half hour after the bake showed a rise above the initial content. Changes in the CO_2 capacity were followed in eight cases; in 3 the capacity fell, in 4 it rose, in 1 it remained unchanged.

In general, the alveolar CO_2 fell below and then rose above normal. The curve for blood CO_2 content did not agree very well with the alveolar CO_2 curves but this may in part have been due to the rapid fluctuation of the latter and to the difficulty of getting coincident determinations. It seems probable that the benefit from either local or general applications of hydrotherapy and heat in arthritis is due largely to the heightened metabolism induced. Further studies are under way, but the suggestion is advanced that the fall in blood CO_2 content is also partly contributary to the improvement.

Studies of the Dissociation Curves for Carbon Dioxide

Observations were conducted on the dissociation curves of blood for carbon dioxide according to the method used by Means, Bock and Woodwell.[13] Eight determinations were carri-

ed out on arthritics and all except one fell within the normal range. The patient who gave the high curve seemed to have a somewhat higher alkali reserve than the average. After exposure to X-ray for the purpose of treating his tonsils the curve for this man was normal but this was doubtless only a coincidence. Determinations of the arterial CO_2 in order to determine the so-called "A point" would be of interest and are planned.

A comparison of the CO_2 content of the fasting blood in 72 arthritics and 12 normals shows that it was negligibly lower in the former, in the following ratio:

72 arthritics.....	53.01%
12 normal.....	55.74%
extremes of arthritics..	43-62
extremes of normals...	47-62

A continuation of these studies is planned or in progress in relation to some of the questions above discussed, expecially the inconclusive data, but various factors make it expedient to publish at this time the result obtained to date by the present collaborators.

Discussion.

The figures on the percentage oxygen saturation of normal persons here recorded are lower than those obtained by most other workers on venous blood drawn without stasis. The oxygen content and therefore the percentage saturation of our normals ran on the average lower than did the normals studied by Lündsgaard[14] and Stadie.[15] This difference may be partly due to the fact that our determinations were all made on fasting blood mostly in the early morning.

The used of a tourniquet introduces variables also, although Lovell and Langstroth* in studying viscosity concluded after the use of a tourniquet for periods of two to ten minutes that changes in the viscosity of whole blood following stasis apparently bear no demonstrable relation to the CO_2 and O_2 content.

Again, table IX illustrates that the effect of the use of a tourniquet was to increase rather than diminish the percentage O_2 saturation (and that this factor can hardly be advanced as accounting for the lower figures of our normals.)

The lower figures, presumably extend alike to both arthri-

* *Jr. Exp. Med.*, 30, 607, 1919.

tics and normals. The difference under discussion furthermore would not account for the contrast noted between these groups during the conduction of a test of lowered sugar tolerance.

In view of the deformity, muscular atrophy and empty veins often encountered in arthritics, it is often difficult or impossible to obtain blood without some preliminary use of a tourniquet. Its use in normals was therefore in some part necessary for control.

There is perhaps room for doubt as to what figures most nearly represent the actual average percentage saturation of the peripheral venous blood of normal persons depending somewhat upon the conditions under which the blood is obtained.

Dr. Glen E. Cullen of the Dept. of Research Medicine, Univ. of Penna. has obtained results comparable to ours on a group of twenty-three supposedly normal students and has kindly allowed us to quote his figures here. Determinations of the venous oxygen percentage saturation were made several hours after a moderate breakfastst and were found to range from 35% to 67.4%, the average being 52.6%. These figures were obtained on blood taken after a preliminary use of the tourniquet and from non-fasting individuals, but even so, they approximate the figures reported here. Figures obtained after eating are definitely and sometimes markedly higher, whether in health or disease, than those determined after a twelve to fifteen hour fast. Dr. Cullen's figures are calculated according to van Slyke's latest corrections.[16]

Failure to detect any constant displacement of the dissociation curves of hemoglobin for oxygen made it advisable to attempt to correlate the high percentage saturation observed, with some other mechanism, such as changes in the rate of blood flow. It was believed that a higher percentage saturation might arise if the blood flow were accelerated through vaso-dilatation, with constant blood pressure, or through vaso-constriction with increased blood pressure. The data do not as yet confirm either of these explanations definitely, but it is of interest to note that in a personal conversation with Dr. E. C. Rosenow he made the statement that in studying the capillary circulation under the microscope in certain animals in which chronic focal infection had been experimentally pro-

duced, there was observed a vaso-constriction. Hooker,[17] Rich and others[18] have furthermore shown that various substances, such as histamine, conceivably resulting from proteolysis have a definite vasomoter influence and the way is open to further experimentation in connection with arthritis along these lines.

Starting with the premise that there might exist in arthritis a difficulty in the oxygen delivery, the higher percentage saturation of oxygen found, together with the high saturation figures which accompany a lowered sugar tolerance, can be regarded as in line with this view although the mechanism may be somewhat different from what had been anticipated. Further work is needed in several directions, however; for example, in relation to blood collected without the use of the tourniquet and in relation to arterial blood, though there is no *a priori* reason to suspect any difference here.

As has been pointed out in a previous contribution (The Nature of Arthritis and Reumatoid Conditions[2]) the particular relevance of these findings for arthritis depends upon a number of facts, one of which is that the joints themselves are structures of poor blood supply and depend upon the serous elements of the blood or their oxidative metabolism. Space will not permit of discussing further considerations in this connection.

The actual proportion of cases of arthritis which may reveal a higher percentage saturation of oxygen in the venous blood will depend somewhat upon the types and severity of the cases studied. It is probable that one could more or less select arthritics who would generally give low or normal figures and those who would give high figures. In general, the higher figures seem to accompany the most severe cases, from the standpoint of the extent of the active arthritis, though there are exceptions to this. Mere chronicity and disability do not constitute criteria of the activity of the process *per se*. Perhaps the most conservative statement to make in regard to these findings is that under the conditions described many arthritics present them, some to a very marked degree. Febrile cases seem to give lower figures. The number of cases of arthritics, in which the high oxygen figures fell with convalescence, is as yet insufficient to permit of sweeping conclusions, but enough have been observed to illustrate that this relation may sometimes exist. The types

in which this does occur seem to be those in which removal of the apparent cause is followed by a general improvement, rather than those in which betterment occurs in the presence of causes still potentially operative.

The impression is formed that the blood gas figures cited bear a relation to the operation of so-called focal infection and that they may be as closely related to this as to arthritis *per se*, which is only one of its several possible expressions. The parallelism which may occur, during a sugar tolerance test, between the high percentage saturation of oxygen and a lowered glucose tolerance on the one hand and the frequent clearcut relation of a lowered sugar tolerance to marked focal infection, on the other, suggest this very definitely.

The experiments here cited have not sufficed to indicate any relation between a high percentage saturation and the rate of blood flow. Such a relation remains a possibility, however, and in view of the parallelism between the high saturation figures and a lowered sugar tolerance, the thought is here advanced that a lowered sugar tolerance may depend in part at least, upon changes in the rapidity of blood flow rather than upon rate of utilization in a more specific sense.

It is to be borne in mind also that some of the negative results following application of this test are almost certainly due to delay or perhaps entire failure of absorption from the stomach. Several such instances occurred in our experience.

Although in a general sort of way the influence of activity and exercise upon the rate of blood flow is pretty well understood as regards normals, this has not hitherto been considered with particular reference to the arthritic.

It is common knowledge to arthritics themselves, and to students of the disease, that they usually suffer most in the night and early morning hours when their physical activity and metabolism are lowest. The majority of cases become more supple and suffer less pain as the day wears on, and these clinical observations are given more basis by the graphic results in the two cases studied. The question of blood flow is still under consideration but it would appear from the former of these two cases and other evidence cited, that the arthritic may present exceptionally low figures as compared with normals. This tends to throw further light upon his dependence on the activities of the day to dissipate some of his symptoms.

A word is perhaps necessary on the mechanism of electric bakes since these in themselves, although often beneficial, produce temporarily some of the disturbed blood findings which the arthritic seems to show. The full mechanism of their action is not clear and space will not permit of discussion here of the increased metabolism which follows. It may be said, however, that a heightened blood flow is accompanied by a rise in the percentage saturation of oxygen, probably because of the rapidity with which the blood passes through the tissue, but it is also to be borne in mind that the total volume of blood delivered to any part in unit time is also increased. The possibility of explaining the high figures for arthritics along these lines was obviously suggested.

It is not clear at the present writing whether the fall in CO_2 in the blood and especially in the alveolar air at the outset of perspiration is due solely to increased pulmonary ventilation or whether it is partly due to the increased elimination of carbon dioxide through perspiration. That elimination occurs to some degree in the latter way is established. These observations suggest that accentuation of this process may afford one of the beneficial factors in such forms of treatment. Haggard's findings that the CO_2 combining power remains unchanged during a hot bath (one subject) were not observed in the present studies (8 cases).

It is the purpose of this contribution to describe only the results obtained, but it is hoped in a later paper to join some of these findings into a whole with the aim of visualizing in greater detail the pathology causing the actual symptoms.

Conclusions.

1. Observations have been conducted upon 77 arthritics and about 40 other cases representing apparent health and various types of disease. The methods of analysis employed consisted chiefly in the study of the oxygen content and capacity of the venous blood; the CO_2 content; the dissociation curves for oxygen and carbon dioxide; the sugar tolerance; and the rate of blood flow in the hands. These were utilized in connection with fasting, resting subjects and also in connection with the influence of food, exercise, external heat, drugs and other factors.

2. The high incidence of a lowered sugar tolerance in cases

of arthritis at large, especially in the more active stage as already described is corroborated.

3. Observations on the blood gases during the conduction of such a test and after making brief preliminary use of the tourniquet show that there tends to be a rise in the percentage saturation of the blood for oxygen, if the tolerance for glucose is lowered. (See charts I to VI inclusive).

4. The average under these conditions of all percentage saturation points in the thirteen arthritics with a low sugar tolerance was 78.37%; of the eight arthritics with normal sugar tolerance was 64.06%, and for the three normal persons with a normal sugar tolerance was 41.81%.

The average percentage saturation at fasting level was:

For the thirteen arthritic cases with low ugar tolerance 76.33%
For the eight arthritic cases with normal sugar tolerance 64.04%
For the three normal persosns with normal sugar tolerance 40.09%

An increased saturation of the venous blood implies a decreased saturation of the supplied tissue.

5. Under the conditions of the experiment, the average percentage saturation for the group of 77 fasting arthritics at all stages of the disease, including advanced convalescence, was higher than it was for 12 fasting normals, in the ratio of 53.68% to 41.71%. In some arthritics the saturation figures reached very high values. The range was from 26 to 97% for arthritics and from 27 to 51% for normals. This difference in the groups could not be explained upon the basis of external temperature, activity, musculature, nutrition or other obvious factors.

6. During the convalescence of 8 cases which showed high percentage figures for oxygen, these figures fell in 6, were essentially unchanged in one, and rose in another. The safest interpretation to make of these findings is that the percentage of oxygen in the peripheral venous blood of fasting arthritics, under the conditions described, is on the average slightly higher and may be very much higher than in fasting normals. The tentative conclusion can be advanced that it tends to return to normal with convalescence or recovery in some cases.

7. Study of the dissociation curves of the blood of 12 arthritics for oxygen showed that they fell in general within normal limits with one marked exception.

8. In eight determinations of the carbon dioxide dissocia-

tion curves of the blood, all but one fell within the normal range.

9. Attempts to correlate a high percentage saturation of oxygen in the venous blood of the arthritic, with changes in the rate of blood flow have not yet substantiated such a relation.

10. Thirteen studies on the rate of blood flow in eleven fasting resting arthritics, as compared with 8 determinations on six normals under the same conditions, give average figures which are about the same for the two groups. The rate of blood flow in the fasting arthritics, however, seems to be less constant and may reach lower figures than is the case with fasting normals.

TABLE IX.

Effect of using a tourniquet.

NAME	Method of taking blood	0_2 Content	0_2 Cap.	% Sat.
Charles Brown Post-operative adhesions Not fasting	No. 1. — No tourniquet.	6.19	20.79	29.79
	No. 2.—Tourniquet on about 2 min. Arm blue.	8.85	19.02	46.55
William Evans Ulcer of rectum Not fasting	No. 1. — No tourniquet.	13.64	19.38	70.38
	No. 2.— Usual technique.	19.45	21.58	90.12
	No. 1. — No tourniquet.	19.25	21.95	87.69
	No. 2.—Usual technique but 15 min. later.	17.97	21.95	81.86
Charley Baldwin Typhoid Convalescent Fasting	No. 1. — No tourniquet.	15.7	20.74	75.69
	No. 2.— Usual technique.	17.64	21.17	83.31
Joseph Franchino Mitral insufficiency Fasting	No. 1. — No tourniquet.	15.28	23.53	64.93
	No. 2.—Usual technique.	15.72	20.99	74.87
William Archibald Mitral insufficiency Not fasting	No. 1. — No tourniquet.	11.51	21.47	53.6 %
	No. 2.—Usual technique.	11.08	20.36	54.42%

NOTE: Except where stated otherwise, the needle was not withdrawn from the vein between samples No. 1 and No. 2.
"Usual technique" means that the tourniquet was left on about ½ minute before sample was collected.

11. Blood studies conducted during a series of seventeen "bakes" on arthritics and normals showed that the oxygen percentage rose in fourteen or 82%, due chiefly to a rise in the content. In general, the alveolar CO_2 fell below normal, coincidentally with the outset of perspiration and then rose above normal after the bake. The curve for blood CO_2 content did not agree well with the curve for alveolar CO_2, but this may have been due to the difficulty of obtaining coincident determinations. The CO_2 capacity varied irregularly in the eight cases in which it was studied.

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INFLUENCE OF GLANDS WITH INTERNAL SECRETION ON THE RESPIRATORY EXCHANGE:

VII. The Possible Influence of Suprarenal Involution in New Born Infants on Heat Production

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This work was undertaken to determine whether any quantitative changes in heat production of infants could be detected which might be associated with the spontaneous involution of the suprarenal cortex that occurs during the first month of life.

The possibility of such an association arose from the demonstration that in rabbits and cats there is a marked chronic increase in heat production when the suprarenal function is sufficiently but sublethally crippled in these animals, provided the thyroid gland is intact. Indeed, the possibility that the naturally occurring destruction of the inner layers of the cortex in new born infants may be comparable to that experimentally induced, must be considered[1, 2].

The extraordinary degenerative changes which take place in the suprarenal cortex of infants during the first month of life were described independently by Thomas[3], Elliott and Armour[4], and Kern[5] in 1911. In 1915, Landau[6] published a monograph on the changes in the adrenal glands from birth to the eleventh year of extra-uterine life based on a study of 87 cases. In 1916, Lewis and Pappenheimer[7] reported their observations on this remarkable involution based on 100 unselected cases from the fifth month of fetal life to and including the third year of extra-uterine life. Notwithstanding these excellent anatomical studies of the lesions, they do not seem to have attracted the interest of pathologic-physiologists or of clinicians.

The anatomical descriptions of the above mentioned observers agree as regards the essential lesions. That the human

suprarenal is unusually large during the latter half of pregnancy has long been known. This enlargement is due to an hypertrophy of the cortex. Shortly after birth (during the first month, according to Kern, and during the second week of extra-uterine life, according to Lewis and Pappenheimer), a massive degeneration of the two inner layers of the cortex begins. This degeneration is characterized by more or less hemorrhage and fatty metamorphosis of the cells. The degeneration is fully established by the end of the second week of life and during the next five or six weeks rapid removal of the broken down cells takes place leaving the relatively thin glomerular layer intact. This layer collapses on to the medulla, and, according to Lewis and Pappenheimer, there is no appreciable increase in the width of the cortex, i.e. regeneration, up to the age of three years.

The physiological significance of this degenerative involution of the cortex is still entirely unknown. Most observers are of the opinion that it is a normal physiological process occurring in all infants and that it cannot be considered as pathologic except when accompanied by excessive hemorrhage (the so-called hemorrhage into the adrenal of new born infants). The fact that degenerative changes similar to those occurring in the main glands also takes place in accessory or aberrant cortical rests strongly suggests, as pointed out by Lewis and Pappenheimer, that the process is a systemic one, acting through the blood stream, as does also the fact that prematurity does not alter the time of onset or the course of the involution in relation to birth.

What is the cause of this cortical destruction? The idea that it occurs to allow the medulla to grow or to increase the area of contact between the cortex and medulla seems superficial and inadequate. The possibility that it is in some way connected with the preparation of the infant for extrauterine life and growth does not appear to have been considered. This conception would suggest that the cortical destruction was a normal physiologic process for the purpose of depressing the activity of the cortex in order to aid in bringing about an activation of many organs both with internal and external secretions, hence falling in the general group of interrelations and correlations of organ activities.

In view of the fact that it is possible to produce a prolonged

increase in heat production by sufficient but sublethal injury to the suprarenal glands in animals with intact thyroids, as shown by Golyakowski[8] in dogs, by Marine and Baumann[9] in rabbits, and by Scott[10] in cats, it occurred to us that this normal destruction of such a large part of the infant suprarenal cortex might also be associated with or closely related to the increase in heat production which begins during the second week of life.

With this in mind, we undertook the study of heat production in infants during the first thirty days of life. The extensive studies of Benedict and Talbot[11, 12, 13], of Bailey and Murlin[14], and of Murlin and Hoobler[15], and many others on the normal heat production of infants, have clearly shown that an increase begins shortly after birth and reaches its maximum intensity ordinarily between the tenth and twelfth months of extrauterine life. These facts were obtained by compiling the data of a large number of babies in relation to age. We have not been able to find any records of daily or repeated heat production measurements on a series of normal babies from birth to the thirtieth or fortieth day of life. For the study of the present problem, viz. whether the suprarenal involution occurring during the first month of life has any influence on metabolism, it was necessary to have repeated heat production measurements on the same babies from birth through the first month of life at least and longer if possible. The studies of Benedict and Talbot[11] on a series of 100 new born babies showed numerous instances where heat production was measured daily on the same baby for the first eight days of life but not longer. These studies by Benedict and Talbot have established among other things, the important fact that after the first 24 hours daily heat production averages are fairly constant for a given baby up to the eighth day, i. e. 660 — 670 calories per square meter; while on the eighth day the average daily heat production in six infants rose to 702 calories per square meter, or an increase of 5.5 per cent. Whether this rise on the eighth day, as noted by Benedict and Talbot, has any relation to the suprarenal involution is of great interest, and from this point of view it is unfortunate that their studies could not have been continued for another week or more.

Material and Methods. Through the courtesy and cooperation of the Sloane Hospital for Women, and of Professor Wil-

liam E. Studdiford and his staff, we have been able to study the heat production on ten full term breast fed "normal" babies, of which seven were studied for more than two weeks.

All heat production measurements were made with the Haldane open circuit apparatus. The modifications required to accommodate babies have been described in a separate paper[16]. The routine procedure for all experiments was as follows: Babies were brought directly from the nursery immediately after being fed and dressed and placed in the chamber. Ventilation (using outside air) was continued until they went to sleep, which during the first week of life usually requires only a few minutes. Older babies are more restless and lie awake longer. As soon as the baby went to sleep the measurement was begun and continued for one hour if the baby remained quiet, or the observation was terminated as soon as it awoke and began to move. Heat production measurements were made on alternate days while the babies were in the hospital throughout the period of observation and then it was necessary to arrange with the mother to bring her baby at an appointed time, so that it could be fed and dressed as usual just before starting an observation. In spite of our efforts, irregularities in the time intervals occurred.

The general data of heat production expressed in calories per kg. per hour for all ten cases are given in Table 3.

Seven cases were observed for more than two weeks, the last heat production measurements being made on the thirty-fourth day of life in two cases, on the thirty-first in one, on the twenty-sixth in one, on the twenty-second in one, on the twentieth in one, and on the seventeenth in one. The time of discharge from the hospital is also indicated in this table. In two instances it occurred on the fourteenth day, one on the fifteenth, two on the twenty-second, one on the twenty-third and one on the twenty-sixth day of life. In only three cases were there significant numbers of observations after discharge. No heat production measurements were made on babies under thirty-six hours old. This plan was followed for several reasons, the more important being to avoid the low heat production occurring in the first twenty-four hours, to allow the house physicians time to observe and decide whether the baby was "normal", and to allow time for the establishment of nursing. In most cases, a supplementary formula feeding

TABLE I.

Baby — E. S.

Date 1922	Weight gm.	Duration of Observation Hour	Average Room Temperature	Average Chamber Temperature	Average Respiration	CO_2 gm.	gm. O_2	R. Q.	Total Calories	Calories per kg. per hr.	REMARKS
May 1	3011	1	22.6	26.2	37	2.02	1.81	81	6.11	2.03	Asleep all of hr.
" 5	3165	1	23.4	27.3	41	2.42	1.86	95	6.46	2.04	" " " "
" 7	3239	1	24.2	28.1	45	2.95	2.26	95	7.88	2.43	" " " "
" 9	3337	1	23.6	27.5	36	3.09	2.17	104*	7.94	2.38	Cried just at end of hour.
" 11	3362	1	27.2	29.0	49	2.66	2.45	79	8.21	2.44	Quiet throughout hr.
" 17	3480	1	23.5	27.2	55	3.25	2.54	93	8.82	2.54	Sleeping lightly
" 22	3765	1	25.6	27.4	50	3.43	2.70	92	9.39	2.49	Quiet throughout hr.
" 24	3740	1	24.4	27.2	43	3.13	2.50	91	8.64	2.31	Asleep all of hr.
" 26	3795	58′	25.5	27.7	38	2.92	2.31	92	8.27	2.18	Cried — Terminated Obs.
" 29	3872	1	24.6	27.2	37	3.22	2.38	98	8.40	2.17	Asleep all of hr.
June 1	3995	1	25.0	27.7	50	3.51	2.63	97	9.23	2.31	Quiet throughout hr.

PROTOCOL I.

Baby E. S., female, white, born April 29, 1922 (4.45 A.M.), weight 3175 gm.
Normal delivery (labor 9 hrs., 30 min.). Grav. i. Wassermann (maternal) negative.
April 30, 1922. Condition good.
This baby received only breast milk.

May 1. Weight 3011 gm., condition good, not nursing well.
Began metabolic study at 9.45 A.M. (i.e. 53 hrs. after birth).
Physical examination by Hospital Staff: apparently a normal baby.
" 2. Nursing well, condition good.
" 5. " " . Metabolic rate.
" 13. Discharged from Hospital.
" 17. Returned for metabolic rate.
" 22. " " " "
" 24. " " " "
" 26. " " " "
" 29. " " " "
June 1. " " " " . Observations discontinued on this date.

The essential data relative to the respiratory exchange in this baby are given in Table I.

* Figured on basis of 100 R.Q.

was given between the twenty-fourth and seventy-second hours of life. A chart made from the average heat production per kg. per hour for all babies in relation to age is given in Figure I. The following two protocols are published in detail.

TABLE II.

Baby — M. M.

Date 1922	Weight gm.	Duration of Observation Hour	Average Room Temperature	Average Chamber Temperature	Average Respiration	CO_2 gm.	O_2 gm.	R. Q.	Total Calories	Calories per Kg. per hr.	REMARKS
May 12	2987	1	22.5	25.4	31	1.82	1.55	85	5.30	1.77	Cried just at end of hr.
" 15	2858	1	23.4	26.4	30	1.75	1.75	73	5.75	2.01	Asleep all of hr.
" 17	2873	1	24.1	26.1	28	2.43	2.33	76	7.73	2.69	" " " "
" 19	2871	1	22.4	25.4	32	2.29	1.89	88	6.49	2.26	" " " "
" 22	3051	1	26.4	28.3	38	2.54	1.98	93	6.90	2.26	Quiet throughout hr.
" 25	3115	1	26.0	27.7	39	2.72	1.90	104*	6.99	2.24	Asleep all of hr.
" 27	3107	1	23.4	26.8	35	2.22	1.92	85	6.46	2.08	" " " "
" 29	3179	1	25.0	28.0	38	2.59	2.16	87	7.41	2.33	" " " "
" 31	3287	1	25.2	27.6	37	2.68	1.86	105*	6.88	2.09	" " " "
June 5	3438	1	26.6	28.8	43	3.26	2.32	102*	8.37	2.44	" " " "

PROTOCOL II.

Baby M. M., female, white, born May 10, 1922 (2.36 P.M.), weight 3175 gm.
Wassermann (maternal) neg. Cæsarean section (on account of valvular disease of heart). (Grav. iii).

May 11. Formula feeding (4 oz. milk + 16 oz. water + 1 oz. lactose).
" 12. Formula feeding as on May 11. Began metabolic study at 3.55 P.M. (49 hrs. after birth).
" 13. Colonic irrigation, nursing, supplementary feeding.
" 15. Slight jaundice, nursing well, supplementary feeding. Metabolic reading. Weight 2858 gm.
" 16. Nursing well, supplementary feeding stopped.
" 17. Abundance of breast milk. Metabolic rate.
" 19. Metabolic rate.
" 22. Metabolic rate. Jaudice disappeared.
" 24. Slight bleeding from cord.
" 25. Metabolic rate.
" 27. " "
" 29. " "
" 31. " "
June 1. Discharged from Hospital.
" 5. Returned for metabolic rate. Observations discontinued on this date.

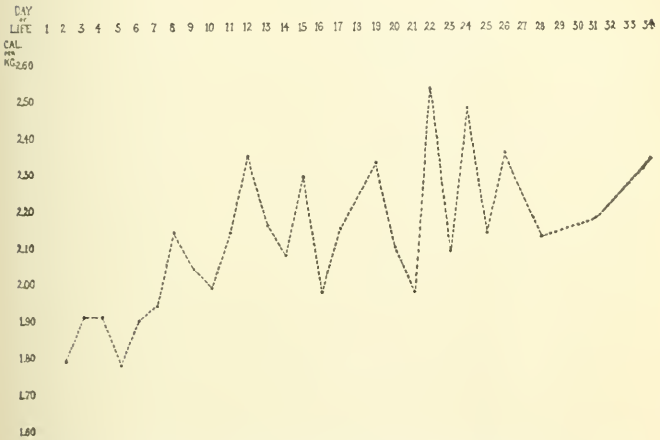
The essential data relative to the respiratory exchange in this baby are given in Table II.

DISCUSSION

Ten babies have been studied for a period of one or more weeks, of which seven have been followed for more than two weeks. It is not possible to form definite conclusions regarding

the possible relation of suprarenal cortex involution to the postnatal rise in metabolism from such a series. Benedict and Talbot[9] give the average heat production during the first week of life as 1.75 calories per kg. per hour. Bailey and Murlin[14] give the average as 1.87. Our average for the ten babies during the first week was 1.88, which approximates very closely the results obtained with closed circuit machines. As pointed out by Murlin[17], the lower average (1.75 calories) reported by

FIG. I.



Benedict and Talbot for the first week of life is due to their including a large number of readings made during the first twelve hours of life when the metabolism may be as much as 15 per cent. lower than on the subsequent days of the first week.

All observers are in general agreement that the average heat production is fairly constant for a given baby between the first and eighth days of life. Then beginning about the eighth day something occurs which brings about a rise in heat production. This rise occurring about the eighth day was observed and emphasized by Benedict and Talbot[11], and is also seen in our series. (See Table I). The fact that the destructive change in the two inner layers of the suprarenal cortex begins about this time, according to Lewis and Pappenheimer, makes its

TABLE III.

Name	Sex	Day of Life																													
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
E. S.	f.	—	2.03	—	—	—	2.04	—	2.43	—	2.38	—	2.44	—	*	—	—	—	2.54	—	—	—	—	2.49	—	2.31	—	2.18	—	2.17	—	—	—	2.31
J. H.	f.	—	1.94	—	—	—	—	—	2.06	—	—	2.43	—	2.09	—	1.99	—	—	2.52	—	1.90	—	2.10	—	2.28	*	—	—	—	—	2.33	—	—	2.40
M. M.	f.	—	1.77	—	—	2.01	—	2.69	—	2.26	—	—	2.26	—	2.24	—	2.08	—	2.33	—	2.09	*	—	—	—	2.44	—	—	—	—	2.06	—	—	—
P. C.	f.	—	2.05	—	—	—	2.09	—	—	2.07	—	2.29	—	*	—	—	—	—	—	—	—	—	—	—	2.03	—	—	2.10	—	—	—	—	—
H. A.	m.	—	1.92	—	—	1.81	—	1.62	—	1.95	—	—	—	—	—	—	—	—	—	2.20	—	2.54	*	—	—	—	—	—	—	—	—	—	—
P. S.	m.	1.80	—	—	—	—	1.68	—	—	1.73	—	—	1.82	—	2.36	—	2.32	—	1.98	2.03	—	*	—	—	—	—	—	—	—	—	—	—	—
A. Q.	f.	—	—	—	—	—	1.95	—	1.73	—	1.93	—	—	*	—	—	2.08	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
D. P.	m.	1.62	1.66	—	—	—	2.02	—	1.97	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
M. R.	f.	—	2.08	—	1.79	—	1.97	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
J. S.	m.	1.97	—	1.92	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Averages		1.80	1.92	1.92	1.79	1.91	1.96	2.15	2.05	2.00	2.15	2.36	2.17	2.09	2.30	1.99	2.16	—	2.34	2.11	1.99	2.54	2.10	2.49	2.15	2.37	—	2.14	—	2.17	2.19	—	—	2.35

* Discharged from Hospital.

relation to the increased heat production suggestive of a functional relationship. When tabulated by weeks, our average heat production figures per kg. per hour were as follows:

1 — 1	days	=	1.88 calories
8 — 14	"	=	2.14 "
15 — 21	"	=	2.15 "
22 — 28	"	=	2.30 "
29 — 34	"	=	2.24 "

A distinct rise, therefore, occurred during the second week notably greater than the combined rises occurring during the next three weeks. The rise in heat production is not progressive nor uniform. Wave-like undulations occur which are possibly comparable with the wave-like cycles of increased and decreased heat production following experimental suprarenal injury, first noted by Golyakowski in dogs and confirmed in this Laboratory on cats and rabbits. Protocol Number 1 illustrates one complete wave and probably the beginning of a second, and extended over a period of three weeks.

It is realized that much more work on metabolism in infants from other angles and by other methods than heat production measurements will be required before probable conclusions may be reached. A quantitative study of the digestive enzymes; of the utilization of food; of heat production in premature infants (Lewis and Pappenheimer state that the suprarenal involution also occurs in them during the second week of extra-uterine life); a study of infantile lactation and the so-called menstrual discharge of infants, all might throw additional light on the possible influence of glands with internal secretion on the postnatal behavior of infants.

Physiological alterations of the most profound nature have to take place within a short time after birth if the baby is to survive. An increase in heat production is one of these physiological adjustments. Alterations in the basal quantity of heat produced probably involve variations in function of all the active tissues of the body. The thyroid-suprarenal cortex interrelationship discussed in this paper is, therefore, but one of a great number of possible interrelationships, directly or indirectly involving the suprarenal cortex influence.

Many other factors than the suprarenal influence may and doubtless do in part account for the progressive increase in heat production beginning during the second week. There is the probability of better utilization of food, of increased tissue

irritability, of an improvement in the quantity and quality of the food, of increased muscular movement, etc. But the influence of all these factors may be closely related to deep seated chemical adjustments taking place through glands with internal secretions.

Conclusions

1. The Haldane open circuit apparatus may be used for accurately measuring the respiratory exchange in new born infants.
2. The average daily heat production for a given normal baby remains fairly constant from the second to the eighth day of life.
3. During the second week of life there is a rise in heat production associated often with the other signs of increased tissue activity.
4. It is suggested that the rise in heat production beginning in the second week of life may be related in some way to the normal destruction of the reticular and fascicular layers of the suprarenal cortex, which also begin at this time.

NOTE: These studies were made at Sloane Hospital for Women, Service of Prof. W. E. Studdiford. We wish to thank Prof. Studdiford, the Hospital Staff and Miss A. I. Byrne for placing the necessary facilities at our disposal and for their advice and cooperation.

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THE EFFECT OF SPLENECTOMY UPON THE RESPIRATORY EXCHANGE IN RABBITS

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The suggestion of a functional relationship between the thyroid and spleen was put forward by Zesas[1] and Credé[2] in 1883, when they noted enlargement and evidence of increased activity of the thyroid gland after splenectomy. The experimental splenectomies of Tauber[3] in 1884 failed to support this view. Pathologists have long recognized that moderate enlargement of the spleen with fibrosis is usually associ- with all forms of goiter. This has, however, been looked upon as part of the general lymphoid reaction seen both in simple and exophthalmic goiter, and it is believed to be a parallel manifestation of the general metabolic disturbance rather than evidence of a functional interrelationship.

Recently, Asher and his pupils have revived the question of a possible functional interrelationship between the thyroid and spleen. Several publications on the effect of splenectomy upon the respiratory exchange have appeared from his laboratory. Danoff,[4] working with white rats, noted a marked and sustained rise in the CO_2 and water output by the lungs beginning within 24 hours after splenectomy and continuing throughout the period of observation—the longest being eight days. The fact that Danoff's rats survived splenectomy only from three to nine days indicates that important factors other than splenectomy were involved. Rats,[5] rabbits[6] and other mammals[7] normally survive this operation indefinitely—a belief held by Aristotle. The significance of the increased respiratory exchange obtained by Danoff in relation to spleen function may therefore be questioned.

Hauri[8] noted a rise in the CO_2 and water excretion by the lungs in two splenectomized rabbits which were independent of variations in the environmental temperature. He also noted a slight increase in the CO_2 output in a splenectomized rabbit

that had previously been thyroidectomized. From these data they conclude that the thyroid and spleen are antagonistic in respect to certain effects on nutrition. The number of animals used was very small, we believe too small to establish a possible thyroid-spleen interrelationship. Further, the O_2 consumption was not computed and in the absence of the respiratory quotient it is not possible to determine the heat value of the increased CO_2 excretion.

The older experiments of Richet[9] and others on splenectomized dogs showing that such dogs required a much greater food intake to maintain their body weight might suggest an increase in metabolism. Smith and Ascham[5] have, however, been unable to obtain evidence of increased appetite or food intake in splenectomized rats.

Asher and Koda[10] were unable to demonstrate any increase in CO_2 excretion in one splenectomized dog.

On account of the variable results reported and because we have been engaged in similar work with other glands of internal secretion it was decided to repeat the studies of Asher and his pupils on the respiratory exchange in splenectomized rabbits. The methods used were similar to those employed in our previous studies on the respiratory exchange. After two preliminary training periods measurements of heat production were begun using the Haldane apparatus as modified by Marine and Lenhart.[11] The animals were last fed 18 to 20 hours before being placed in the chambers. It has been found that a two hour period frequently repeated is the most certain means of evaluating the movement factor in heat production of animals. Four to six control measurements were made on each rabbit over a period of two or three weeks to establish normal levels. If the results of these measurements did not check within ten per cent. the animals were rejected. Rabbits having good control heat production measurements were then subjected to splenectomy* and the respiratory exchange measured on the second day after splenectomy and on alternate days thereafter for two or more weeks.

* In removing the spleen in rabbits an incision is made extending from the intercostal space between the last two ribs on the left side downward and inward a distance of about 5 cm. The spleen is readily delivered through this wound and after elevating it slightly the long mesenteric attachment is ligated in three and sometimes four masses without traumatizing or interfering with the blood supply of the closely attached pancreas. The mesentery is then cut with fine scissors as close to the spleen as possible.

The general data of these experiments are given in Table 1 and two protocols typical of the group are given in detail.

TABLE 1

Rabbit No.	Age	Sex	Date of Splenectomy	Average Normal Metabolism: Calories per kg. per hr.	METABOLISM AFTER SPLENECTOMY						Average Metabolism 1st 6 days after Splenectomy	Percentile Change
					2nd day	4th day	6th day	8th day	10th day	12th day		
274	adult	m.	11- 8-21	2.14	2.43	2.20	2.41			2.19	2.34	+ 9
275	"	m.	11- 8-21	2.28	2.53	2.34	2.36	2.29		2.46	2.41	+ 6
276	"	m.	8- 2-21	2.23	2.23	2.25	2.46	2.22	2.24		2.31	+ 4
277	"	m.	8- 2-21	2.50	2.20	2.31	2.06	2.39	2.33	2.14	2.19	+12
278	"	f.	8- 2-21	2.08	2.03	2.17	1.93	2.26	2.11	2.82	2.04	— 2
283	"	f.	11- 8-21	2.20	2.64	2.49	2.63	2.14	2.02	2.23	2.58	+17
291	"	m.	1-18-22	2.43	2.78	2.78	2.55	2.38		2.57	2.70	+11
306	6 mo.	f.	1-18-22	2.71	2.84	2.96	2.92	2.75		2.84	2.90	+ 7
310*	6 "	f.	1-31-22	2.65	2.67	2.98	2.96				2.87	+12
312†	6 "	f.	1-31-22	2.50	2.90	2.78	2.70		2.96	3.06	2.79	+12
313	6 "	f.	1-31-22	2.77	3.07	3.18	3.38		3.27	3.03	3.21	+16
361	91 da.	m.	7- 6-22	3.79	3.74	3.70		3.61	3.52	3.66	3.72	— 2
362	91 "	m.	7- 6-22	3.67	3.89	3.86		3.64	3.07	3.44	3.87	+ 5
363	98 "	m.	7- 6-22	3.09	3.34	3.08	3.25	3.21	3.26	3.34	3.22	+ 4
365	102 "	m.	7- 6-22	3.04	3.46	3.12	3.55	3.24		3.36	3.37	+11
366	102 "	f.	7- 6-22	3.78	4.14	3.95	3.76	3.64		3.55	3.95	+ 4

* Killed (Pneumonia).
† 2-12-22 Gave birth to young.

Sixteen rabbits were used. One (310) was sacrificed on account of pneumonia nine days after splenectomy. The remaining fifteen have survived indefinitely. The operation, performed under ether anesthesia was short and uncomplicated in fourteen. In one (278) the mesentery was unusually short and there was some shock from traction. In another there was slight hemorrhage, possibly 3 to 4 cc. from puncturing a vein in passing the ligature. Both these animals recovered rapidly and ate their full rations on the day following the operation. All wounds healed without infection. The possibility of seasonal variation and variation due to age were considered, thus, three rabbits were splenectomized in August, three in November, five in January and five in July. Three of the four with significant rises, i. e. above 10 per cent. occurred during the colder months. Seven of the rabbits used were adults of unknown age. Two of these showed rises in the respiratory exchange during the first six days after splenectomy of 11

TABLE 2.

Rabbit 306

Date	Room Temperature	Weight of Rabbit	CO_2 in grams, 2 hrs.	O_2 in grams, 2 hrs.	R.Q.	Total Calories, 2 hrs.	Calories per kgm. per hr.	
1921		gms.						
Dec. 2	24.5	1833	3.150	2.860	80	9.62	2.63	Quiet
" 7	21.8	1847	3.310	2.770	87	9.47	2.56	"
1922								
Jan. 5	21.8	1949	3.430	3.390	74	11.15	2.06	Dec. 8-25 mg. KI
" 12	21.0	1992	4.220	3.220	95	11.27	2.83	Slightly restless
" 17	24.0	1954	3.510	3.060	83	10.41	2.66	" "
" 20	21.5	1916	3.940	3.150	91	10.88	2.84	Jn. 18 Splnectomy
" 23	20.2	2000	4.360	3.420	93	11.84	2.96	
" 25	22.0	1954	3.880	3.350	84	11.40	2.92	
" 27	23.6	1938	3.690	3.110	86	10.65	2.75	
" 30	25.5	1880	3.560	3.140	82	10.67	2.84	
Feb. 1	22.4	1886	3.510	2.910	88	9.95	2.65	

Protocol 1. Rabbit 306. Female, aged 6 months.
Dec. 2, 1921. Began metabolic studies. Weight 1833 gms.
Jan. 18, 1922. Under ether removed spleen.
Jan. 19. Ate all of ration, apparently normal.
Jan. 26. Wound healed, stitches removed.
Feb. 1. Last metabolic rate for the spleen-thyroid interrelationship.
Feb. 2. Removed thyroid gland and began other studies. The data of the respiratory exchange are given in Table 2.

and 16 per cent, respectively. In view of the observation by Marine and Manley[6] that autotransplants of the spleen with splenectomy in adult rabbits did not show any significant growth, while similar transplants in young rabbits showed marked growth, and the suggestion that the spleen was a more important organ in young animals, it was thought that possibly splenectomized immature rabbits might also behave differently in respect to their respiratory exchange. Nine healthy young animals born and reared in the Laboratory were used for the further study of this problem. Four rabbits were between six and seven months old, two were 102 days, one 98 days and the remaining two 91 days old. Apart from the higher metabolic rates due to age these rabbits did not show results differing essentially from those obtained with adult animals. Six of the 16 animals showed significant increases in heat production varying from 11 to 16 per cent during the first

TABLE 3.

Rabbit 313

Date	Room Temperature	Weight of Rabit	CO_2 in grams, 2 hrs.	O_2 in grams, 2 hrs.	R.Q.	Total Calories, 2 hrs.	Calories per kgm per hr.	
1922								
Jan. 17	23.0	1991	4.190	3.050	100	10.76	2.71	Quiet
" 19	24.0	1944	3.920	3.060	93	10.64	2.74	Slightly restless
" 24	21.5	1986	4.220	3.210	96	11.18	2.82	" "
" 26	21.0	1977	4.030	3.240	90	11.22	2.84	" "
Feb. 2	23.2	1912	4.220	3.400	90	11.75	3.07	J. 31 Splenectomy
" 4	20.6	1983	4.790	3.610	97	12.59	3.18	Quiet
" 7	22.5	1964	4.770	3.870	90	13.28	3.38	"
" 11	22.8	2028	4.920	3.810	94	13.25	3.27	"
" 16	19.0	1991	4.110	3.540	84	12.08	3.03	
" 20	23.2	2024	4.190	3.330	92	11.47	2.83	
" 24	20.6	2044	4.950	4.130	87	14.16	3.46	
Mch. 3	22.0	2074	4.730	3.550	97	12.43	3.00	
" 10	24.0	2093	4.210	3.140	98	10.98	2.62	
" 14	22.4	2187	4.520	3.320	99	11.70	2.67	
" 21	21.4	2129	4.210	3.360	91	11.62	2.73	
" 28	24.0	2251	4.300	3.620	86	12.41	2.76	

Protocol 2. Rabbit 313. Female, aged 6 months.
Jan. 17, 1922. Weight 1991 gms. Began metabolic studies.
Jan. 31. Under ether removed spleen.
Feb. 1. Ate full ration, apparently normal.
Mch. 28. Last metabolic rate for the spleen-thyroid interrelationship.
Apr. 5. Removed most of R and L thyroid lobes and began other studies. The data of the respiratory exchange are given in Table 3.

week after splenectomy. One of these increases occurred in a rabbit dying of pneumonia on the ninth day after splenectomy and on the basis of heat production studies on several other rabbits with pneumonia (unpublished), the rise may properly be ascribed to the pneumonic infection. In another rabbit showing increased respiratory exchange splenectomy was done on the eighteenth day of pregnancy. Similar increases in heat production (unpublished) regularly occur in pregnant rabbits without splenectomy. A significant increase in metabolism was therefore obtained in four of fourteen uncomplicated splenectomies or 29 per cent. In these four cases the average increases in heat production during the first week were 11, 11, 16 and 16 per cent respectively. In three of these the heat production had fallen to the normal range

on the eighth day, while in the other it was still 14 per cent above its normal average at the end of the second week but fell to the normal range during the third week. Nothing in the subsequent behavior of this animal has suggested any cause for the sustained rise. The animal is in good health (ten months later) although it has been subjected to several other experimental procedures.

Discussion

We have been unable to confirm the observations of Asher and his pupils that splenectomy in rabbits causes a significant increase in metabolism. Slight increases were observed in four of fourteen rabbits lasting six days in three instances and two weeks in the other. The spleen probably has some influence on metabolism, but these experiments do not justify one in drawing any conclusion in regard to its possible influence on heat production nor in assuming a thyroid-spleen interrelationship. As in all other experiments in which the thyroid may be involved, the uncontrolled use of iodin except in amounts that may be present in the food was excluded. Perhaps the criticism might be made that the thyroids of all the rabbits should have been standardized by the administration of a few milligrams of iodin, since this is the best method of controlling the variable physiological and pharmacological activity of the thyroid. In this locality (on the seacoast) in our experience it has proved unimportant. Age and sex have no influence on the effects of splenectomy on heat production. As regards season, it should be pointed out that three of the six rabbits splenectomized during the cold months showed a significant rise while only one of the eight rabbits splenectomized during the summer showed a rise. Trauma, shock and possibly slight hemorrhage incident to splenectomy were without influence.

Conclusions

1. Uncomplicated splenectomy caused a significant rise in heat production in four of fourteen rabbits or 29 per cent.
2. We are not justified at present in assuming an antagonistic action of the thyroid and spleen.

Note: The respiratory exchange measurements were made by Miss Anna Cipra and Miss B. H. Lowe to whom we wish to express our thanks.

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ANIMAL EXPERIMENTS ON CERTAIN PHASES OF THE LYON-MELTZER METHOD OF BILIARY DRAINAGE

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Since Lyon's[1] first publication in 1919, great interest has been manifested in non-surgical biliary drainage, a subject which has since been extensively reviewed in literature. In addition to the many publications of Lyon we need only to refer to the articles of Brown,[2] Smithies,[3] Whipple,[4] Simon,[5] Sachs,[6] Friedenwald and Morrison,[7] Levine,[8] White,[9] Niles,[10] Einhorn,[11] Crohn, Reiss and Radin,[12] Dunn and Cornell,[13] Basler, Luckett and Lutz,[14] and many others.

Most of the work published has been largely clinical in character, while comparatively little has been accomplished experimentally in animals.

As far back as 1887 Oddi described a set of muscular fibres surrounding the terminal portion of the common bile and pancreatic ducts. While the existence of such a mechanism had been previously suggested by others, Oddi[15] demonstrated definitely in animals the presence of a set of circular muscular fibres surrounding the common bile duct, acting as a sphincter, and entirely separate from the circular fibres of the muscular coat of the duodenum.

Hendricksen[16] later confirmed the findings of Oddi in animals and was able to demonstrate the presence of Oddi's sphincter in man.

Mann's[17] publication on the effect of the removal of the gall bladder on the sphincter of Oddi are well known. This observer has demonstrated in dogs that the sphincter will resist from 100 to 150 mm. of pressure, but after removal of the gall bladder it can only resist 40 mm. of water pressure. He also showed that a reflux of contents from the duodenum into the ducts was impossible, inasmuch as the orifice of the duct is surrounded by a fold of mucous membrane which resists a large amount of pressure when an attempt is made to force fluid into the ducts.

Herring and Simpson[18] demonstrated on animals, including monkeys, that the resistance of the sphincter was equivalent to a water pressure of from 200 to 300 mm., while Archibald[19] found that it would sustain a pressure of about 600 mm. within the duct.

It was McMhorter[20] who first demonstrated that a reduction in the resistance of the sphincter of Oddi took place to the extent of from 50 to 100 mm. of water, after the application of a 25 per cent magnesium sulphate solution to the ampulla, which did not occur after a peptone solution.

The innervation of the gall bladder and bile ducts was studied by Doyen[21] experimentally. He attempted to demonstrate that stimulation of the central end of the splanchnic nerve brings about relaxation of the sphincter and gall bladder, while on the other hand stimulation of the peripheral end of the splanchnics causes contraction of the gall bladder and bile ducts. He also noted that stimulation of the central end of the vagus produced contractions of the gall bladder with relaxation of the sphincter of the common ducts and concluded that there was an interrelationship of the gall bladder and Oddi's sphincter (crossed innervation of Meltzer).

The work of Bainbridge and Dale,[22] however, is not in accord with the conclusion drawn by Doyen. These investigators observed that the invariable result of the stimulation of the splanchnics was a relaxation of the gall bladder while stimulation of the end of the vagus produced always only a contraction of the gall bladder.

In a series of experiments only on human beings, Einhorn[11] has attempted to prove that substances other than magnesium sulphate, such as sodium citrate, chloride, sulphate, etc., when locally introduced into the duodenum increase the flow of bile from the common duct equally well and give rise to a play of colors from light to dark and back to light again, and that the dark colored bile is produced by an undefined action of the liver due to the absorption of the sulphate radical of the magnesium salt. However, the results of these experiments have by no means been confirmed; in fact they have been rather disproved by the observations of Lyon.[25]

Hartman[23] has demonstrated in his experiments on dogs in which a high ligature of the cystic duct had been made, that several weeks or months later at autopsy in a number of instances a definite dilatation was observed at the end of the cut cystic duct in which a more static darker bile was noted. This fact may account for the dark bile obtained in certain cholecystectomized individuals.

Rous and McMasters[24] have demonstrated that the gall bladder has the function of concentrating liver bile to a marked degree (ten times its volume of liver bile), thus providing a safety valve; for otherwise spontaneous rupture of the gall bladder might occur. When this functional capacity of the gall bladder has been exhausted or interfered with further concentration of the bile may occur in the ducts.

These investigators have also observed that from 75 to 90 per cent of the total secreting area of the liver must be obstructed before jaundice can be produced in experimental animals. When the obstruction occurs in cases of cholecystectomized animals its storage and concentration function must be performed by the ducts and later by the liver.

Of interest in connection with our own work is the evidence of

Whipple,[4] who observed that in about 50 per cent of his cases one or more varieties of bacteria found in the preoperative duodenal bile could be demonstrated in the gall bladder bile or gall bladder tissue.

Crohn, Reiss and Radin,[12] as the result of an elaborate set of experiments on dogs, deny the existence of a real anatomic sphincter, though physiologically they admit that a sphincteric action of the papilla of Vater is demonstrable. They noted "that during digestion in the dog the flow of bile from the papilla was slow, but practically continuous and consisted of bile from the liver. By drawing the finger even gently across the papilla or by application of faradic stimulation or chemical irritants, it was seen that the sphincter promptly closed the duct." "An interval between 10 and 30 seconds elapsed during which the papilla was erected like a mammary nipple. Then a relaxation took place and the flow of the bile was re-established. Not only the papilla but also the surrounding segment of duodenum responded to the stimulus. If the stimulus was strong enough the whole segment became tonically contracted; if weaker, only the papilla and adjacent musculature. Thus we were able to demonstrate a definite sphincteric action, though not actually a certain anatomic sphincter."

Crohn[13] and his co-workers injected into the gall-bladder cavity of dogs narcotized with chlorbutanol a solution of methylene blue in physiological salt solution. After opening the duodenum, the papilla was exposed for observation. "It was noted that though the flow of bile is almost continuous after meals, this bile consists entirely of liver bile, the blue discolored gall bladder bile not appearing at all except when manually expressed. Cholagogues and solutions of salines and peptones had a tendency to encourage this flow of liver bile; but we found no agent applied to the duodenum that caused the expulsion of the gall bladder contents." "By applying a concentrated solution of magnesium sulphate to the mucosa of the duodenum in the fasting dog, no bile of any kind was observed to pass out of the papilla. A slight flow of light yellow golden bile, apparently of liver bile, followed but there were no contractions of the gall-bladder noted and no blue discolored bile was observed."

Auster and Crohn,[27] in a more recent publication giving conclusions drawn from experimental observations, are of the opinion that the view generally maintained that the gall bladder is an actively contracting organ, filling and emptying rhythmically, should no longer be held. According to these observers the flow of bile originates in the liver, passing mainly through the ducts into the duodenum without reference to the gall bladder, and the gall bladder itself does not appear to participate actively in the biliary excretion. The outflow of the gall bladder therefore appears in the form of an incontinence or overflow.

According to Lyon,[28] the explanation of the observations of Crohn and his co-workers lies in the fact that the "antagonistic innervation" of the gall bladder is a mechanism easily disturbed, which might likely be inhibited or even abolished by the effect of a general anesthesia.

Bassler, Luckett and Lutz,[14] in a series of experiments on ten human

beings who were examined during operation with the duodenal tube *in situ*, were unable in any instance "to prove any vermicular action on the part of the gall bladder, or any visible reason to suggest that any contraction took place or that the characteristic dark colored bile when obtained, was from the gall bladder." They further observed that the darkest colored bile is recovered from the gall bladder itself after manually expressing the contents.

From the foregoing observations, it may readily be noted that a considerable amount of experimental work has already been published, notably on human beings, on the Meltzer-Lyon method of non-surgical gall bladder drainage and allied problems. Yet we are still of the opinion that more experimental detailed work is required to settle some of the contested phases of this method.

It is realized that there are great differences in animal physiology and clinical pathology and especially the power of resistance to various microorganisms, but we feel that parallels may be drawn at least in some instances.

Certain difficulties are at once encountered in the applications of this method to dogs. In the first place it is practically impossible to pass a duodenal tube through the oral route in these animals. We have tried it out exhaustively, utilizing metal obturators within the tube and simultaneously feeding with broth, hot water, placing the dog on its right side for hours and in various other positions without avail. Various tips were utilized but in no instance, regardless of the size of the dog, were we able to pass the pylorus without recourse to a laparotomy. Under these conditions, the operator would feel the tube in the stomach. The obturator would be withdrawn and the tube "milked" into the intestine manually.

Contrary to clinical experience and in spite of great care in handling the intestines and tubes, frequent hemorrhages from the intestinal wall would occur, and it often became necessary to irrigate the intestines with cold water in order to check the blood flow. This was observed when the wire obturator was not employed. It was thought that sudden dilatation of the intestinal walls might have produced a rupture of the delicate capillaries. Accordingly the washings were given gently by means of gravity, often without occasioning any marked improvement of this condition. Furthermore it was frequently found impossible to obtain bile at all through this route even under the most favorable circumstances. Later

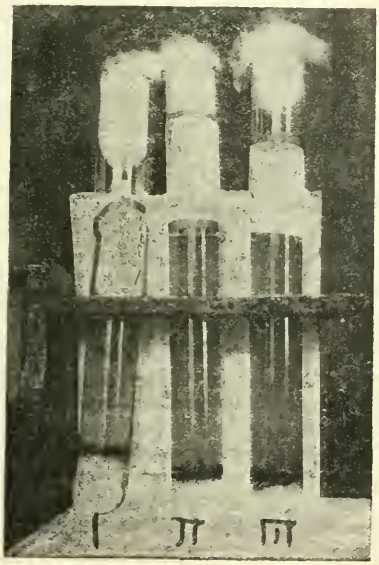
most of the work was accomplished through gastrostomy openings.

Without prejudice as to the exact mechanism by which magnesium sulphate acts upon the gall bladder and the sphincter of Oddi, we tried to estimate quantitatively the flow of bile (and duodenal contents from a given sector of the duodenum) when stimulated by this salt.

Technic.

Under ether, an anterior gastro-enterostomy was performed on a large dog. A small rubber tube was inserted into the duodenum direct-

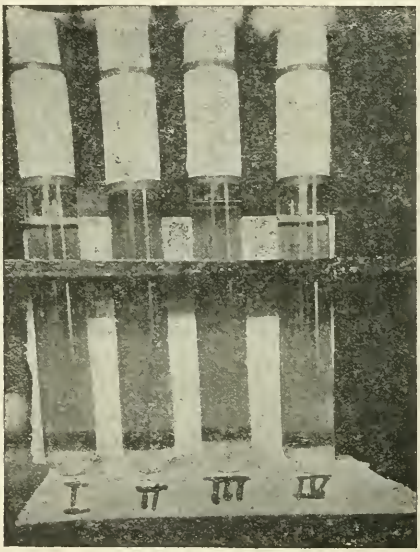
CHART I.



I. Duodenal drippings from starving dog.
II. Duodenal drippings after 20 cc. of broth had been administered.
III. Duodenal drippings three days later following administration of broth at the same interval in addition to the local stimulation with magnesium sulphate.

ly opposite the ampulla of Vater. The intestine was then tied off on each side as close as possible to the tube, leaving a closed pouch of intestine about 2½ inches long. The following day the dog seemed to be in excellent condition. At this time a test tube (padded externally with cotton) was passed over the rubber catheter and the dog encased in a special abdominal harness and allowed to run about the room. The duodenal contents were then collected at hourly intervals. The total quantity of secretion obtained was measured and then poured into a test tube containing a preservative. This was simply left in the bottom of the test tube to present the bile ring more clearly, as will be observed in the accompanying photographs. It was obviously impossible to measure the bile rings quantitatively. The difference in depth, however, is readily shown. Our clearest and most striking result was obtained in dog 5, as illustrated below.

CHART II.



I and III. Duodenal drippings one hour after feeding with broth.
IV. Duodenal drippings during second hour after feeding with broth.
II. Duodenal drippings one hour after feeding with equal quantity of broth to which a saturated solution of magnesium sulphate had been added.

Tube No. 1 contained drippings from a starving dog (1 hour specimen); 14 cc. was the total amount of fluid obtained.

Tube No. 2 showed the result after 20 cc. of broth had been administered by mouth (1 hour specimen); 19.5 cc. was the total amount of fluid obtained.

Tube No. 3 was obtained 3 days later (1 hour specimen), after broth had been injected into the stomach and 4 cc. saturated magnesium sulphate solution injected directly through the tube; 29.5 cc. was the total amount of fluid obtained (from which 4 cc. magnesium sulphate must be subtracted) leaving in all 25 cc. of total fluid.

It will be noted that specimens 2 and 3 are from the same dog in the same phase of digestion, which had been given equal quantities of broth and at approximately the same temperature. The bile ring in specimen 3 was obviously wider. It may be stated here parenthentically that the bile was returned clear and did not appear to be infected. The dog's temperature at this time was normal.

One hour controls were made as shown in specimens 3 and 4. Specimen 3 presents the washings 1 hour after feeding with broth, when 19 cc. of total fluid was obtained. Specimen 4 was obtained 2 hours after feeding broth; 18 cc. of fluid was secured. It will be noted that the bile rings are approximately the same in size, that is that the output during the 1st and 2nd hours of digestion is approximately equal. The total duodenal discharge, however, decreases from 19 to 18 cc. This agrees with Crohn and Auster's[12] work who state that "during digestion in the dog the flow of bile from the papilla was slow and practically continuous." According to our work, then, any possibility of increasing the digestive curve being eliminated by means of the controls, magnesium sulphate definitely increases the flow of bile when applied locally. This, of course, is entirely at variance with the observations of Bassler, Luckett and Lutz[14]. In an effort to ascertain whether this result was due to a local or central action the following experiment was performed. Specimens 1 and 2, below, show the duodenal drippings from a dog fed by mouth (1) broth; (2) warm broth together with warm magnesium sulphate solution, on consecutive days, each at the same intervals, i. e., one hour after feeding and at the same hour in the morning. With No. 1, obtained one hour after feeding with warm broth, 18 cc. of total fluid was secured. With No. 2, one hour after feeding an equal quantity of warm broth together with a saturated

solution of warm magnesium sulphate, 22 cc. of total fluid was obtained. If anything the bile ring in No. 1 is a trifle wider. The total duodenal secretion is, however, increased by the magnesium sulphate. We feel justified in concluding that a saturated solution of magnesium sulphate applied locally to the duodenum in dogs under experimental conditions increases the flow of bile. Our work does not support the theory of a central mechanism.

Furthermore, it appears that a saturated magnesium sulphate solution increases the flow of the intestinal juices, acting either locally or centrally. The former finding may be explained on the basis of the well known cathartic action of concentrated saline purges in the intestine, which since the days of Matthew Hay has been known to attract quantities of fluid to the bowel. However, we have repeatedly seen an increase in the intestinal secretion where magnesium sulphate was fed by mouth and the biliary apparatus and the duodenum were absolutely cut off from any possibility of local action. We are not prepared to argue the exact mechanism involved, but will content ourselves by showing the quantitative results.

At this point, however, it is well to observe that in our series of 34 dogs we have never been able to observe an actual contraction of the gall bladder. We stress this point, as Sachs[6] and Lesner[28] have reported contractions of the gall bladder following stimulation with magnesium sulphate. It has been our routine to watch for this under various stages of anesthesia with the tube *in situ*, in an effort to settle this point, but no contraction could be observed. We have also attempted upon several occasions Crohn's experiment of injecting the gall bladder with methylene blue and then stimulating, but have never been able to recover the dye. Perhaps Lyon's theory, viz, that the antagonistic innervation of the gall bladder is a mechanism easily disturbed, which might likely be inhibited or even abolished by the effect of a general anesthetic, explains this observation. It is also obvious that nerve endings have been cut and normal anatomical relations altered.

The normal A, B, and C sequence of biliary flow has never been observed in dogs. Occasionally we have seen changes, but they were not constant, and as mentioned above the color was frequently obscured by blood. Due to this fact and the

anesthetic mishaps we were able to secure a clear biliary picture in about every third dog.

Consequently, we were not surprised to find that the biliary content obtained after stimulation with a concentrated magnesium sulphate in a normal dog was identical in appearance with that secured from a cholecystectomized dog. From either a cholecystectomized dog or a dog with the gall bladder tied off, our biliary fractions were absolutely similar in every case. Some of these have been kept for several months in preservatives.

In turning to the bacteriological phase of this subject, difficulties were encountered which cost us months of perplexity. Numerous attempts were made to infect the gall bladder of dogs with various organisms.

Our usual plan was to open the gall bladder, insert a foreign body, i.e., a bit of wire, a small stone, etc., and then inject the bacterial culture. This was accomplished in various ways, scarifying the mucous membranes of the gall bladder, infiltrating the gall bladder walls, and on several occasions utilizing material from infected human gall gladders. Our controls (that is to say, bile taken from the gall bladder before infection) and the gall bladder contents after infection were always identical in color and consistency.

Virulent bacteria, such as the hemolytic streptococci, various strains of staphlococci and typhoid bacteria, both singly and in combination, were tried with the same result. The dog would become very ill, judged from clinical signs and by a rise in temperature, but infected bile, that is in the sense of being turbid, was never recovered.

Finally Dr. Charles W. Judd in a series of cultures showed that dog bile was hostile to any of the organisms which we employed, the bacteria dying off in something like 48 hours. However, it was frequently possible to recover the offending organism, e.g. the hemolytic streptococcus and typhoid bacteria, before inhibition was complete.

Apriori, it was not reasonable to assume that a dog could be infected through its bile with typhoid organisms, etc., and apparently this is a fact well known to bacteriologists. Harvey Cushing also drew attention to this fact in 1889. Unfortunately this publication was overlooked until late in our work.

From these observations we were inclined to the conclu-

sion for a long time, that infected bile need not necessarily be turbid, that is in the acute stages of infection. According to Gay and Claypoole,[26] similar bacteriological conditions pertain to the bile in cats.

With rabbits the results were more encouraging. Before instituting any work *in vivo* we found that typhoid bacteria grew in rabbit bile under laboratory conditions. Attempts were made to infect the rabbits both through the intravenous route and directly into the gall bladder. Every rabbit infected directly died within 24 hours with swollen and blackened abdomen. The gall bladder contained a thick, creamy, foul smelling secretion containing typhoid bacteria in abundance.

Our technic and results of some of our successful attempts are as follows:

Technic: No attempt was made to pass the duodenal tube through the mouth. A gastrostomy was performed and a rubber tube inserted into the duodenum. A typical experiment performed on July 13 is noted as follows, the bacteriological work being performed by C. W. Judd.

Rabbit No. 2. Typhoid bacteria injected directly into the gall bladder; gastrostomy performed and tube inserted into the duodenum. No attempt was made to do this work under sterile conditions, as we were looking only for typhoid organisms which could be easily identified under Endo plates; 6 fractions were returned after an interval of one hour. Typhoid organisms were recovered from the following samptes: No. 1, duodenal secretion aspirated through tube; No. 2, sterile water injected through tube; No. 3, magnesium sulphate injected; No. 4, magnesium sulphate injected, gall bladder contents manually expressed. Specimens No. 5 and 6 were obtained directly from the gall bladder, the gall bladder being tied off and cultures of the contents made on Endo plates. These contained colon bacilli.

Rabbit No. 3. This rabbit was infected through the intravenous route and the same experiment performed:

No. 1. — Duodenal contents, 12 minutes interval, after injection found sterile.

No. 2. — Sterile water washing of the duodenum after 14 minutes; still sterile.

No. 3.—Magnesium sulphate instillation into duodenum, 15 minutes, sterile.

No. 4. — Gall bladder culture at 20 minutes, suspicious.

No. 5. — Gall bladder culture at 22 minutes, colon bacilli obtained.

Gay and Claypoole[26], by utilizing the intravenous route were able to recover the typhoid organism in 5 minutes after inoculation from the gall bladder, and state that the optimum growth is obtained in an hour. We were unable to confirm this finding. It is obvious therefore that in a bile supporting

the growth of typhoid organisms, it is possible to identify the bacillus by means of the intestinal tube or a modification of the same. The rabbit's bile is similar to human bile in that it supports typhoid growth. Further work with other organisms is contemplated.

It has been already suggested that clinically this method will be valuable in detecting typhoid carriers. We feel that our work seems to encourage its prosecution.

Conclusions.

1. Magnesium sulphate quantitatively increases the flow of bile when applied locally to the duodenal mucous membrane near the gall bladder opening.

2. The bile flow is produced not by a central action but definitely by a local mechanism. The total intestinal secretion is increased either by central or local action following the instillation of magnesium sulphate, a curve which the bile flow itself does not follow.

3. Contraction of the gall bladder, although carefully watched for, was never noted. This may be due to the fact, as Lyon points out, that the innervation of the gall bladder musculature is a mechanism easily disturbed, which might likely be inhibited or even abolished by the effect of a general anesthetic.

4. Finally in susceptible animals offending organisms, such as typhoid bacilli, may be recovered by means of the duodenal tube or a modification thereof.

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STUDIES OF THE VITAMINE POTENCY OF COD LIVER OILS

III — The Potency of Pollock Liver Oil — Early Summer Oils.

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According to the definition of the Pharmacopœia of the United States, medicinal cod liver oil is a "fixed oil obtained from fresh livers of Gadus Morrhua Linne and of other species of Gadus (Fam. Gadidae)." From this definition it would seem that cod liver oil may be a mixture of oils obtained from the livers of any of the species of "Gadus", and furthermore a product labeled pure cod liver oil but consisting entirely of oils from livers of other fish of this species, would seem to meet the specifications of the Pharmacopœia.

In order to secure first hand information as to the composition of commercial medicinal cod liver oil a limited survey was made of the cod liver oil industry. Replies to personal inquiries varied all the way from the statement of an oil dealer who would "guarantee to supply cod liver oil which was obtained from cod livers only", to the statement of a fisherman who said, "I don't believe there is a gallon of cod liver oil in this country that doesn't have some other fish liver oils in it. When a man goes fishing he takes what's on his hooks and when he cleans his fish any liver that will make oil goes into his bucket and he sells his livers to the oil man, no questions asked. Anyhow, after the livers have been in the bucket an hour or two the oil man can't tell cod livers from pollock, or hake, or other fish livers".

In view of this situation it has seemed highly desirable to ascertain what fish liver oils may occur in commercial cod liver oil, and to determine the vitamine potency of such fish liver oils in order to secure definite data as to whether the addition of these oils yields a product of higher or lower vitamine content than that of true cod liver oil. With this

purpose in mind a series of experiments has been conducted to determine the actual vitamine potency of liver oils of a number of fish. In this locality the fish that is probably most frequently taken when fishing for cod fish is pollock, and the present paper is concerned with a series of experiments which was made to determine the potency of pollock liver oil.

To eliminate all uncertainty as to the origin of the pollock liver oils under investigation the author went to Rockport, Mass. and secured a supply of pollock livers as they were taken from the fish which had been caught a few hours previous in nearby fishing grounds. These fish were brought to the docks unopened, called "round fish" by the fishermen, and the livers were removed under the supervision of the author and were then taken directly to the laboratory, where they were iced until the following morning, when they were rendered by a simple rendering process which has been described in detail elsewhere[1].

Two samples of pollock liver oil were used in the tests reported below. One was oil obtained June 8, 1922, from livers of fish that were in a rather emaciated condition. These fish had evidently just come to the fishing grounds and appeared to have had insufficient food for some time previous, during which time they had in all probability been migrating. When they were opened practically no food was found in the alimentary tract. The livers taken from them were very dark, and, as compared with those obtained from fish caught later in the season, had a decidedly lower fat content. The second oil was from pollock caught July 18, 1922 on the same fishing grounds. These fish were in much better physical condition than those caught early in June. They were quite plump, and when cooked the edible portion of their bodies seemed more palatable than that of the June fish, due probably to a larger amount of fat in the muscle tissues. This improved physical condition evidently resulted from a more generous diet, for when they were opened a good many small herring were found in the alimentary tract. The livers obtained were lighter colored, larger and more plump and contained a larger percentage of oil than those of the June pollock. The two pollock liver oils were analyzed to determine the nature of their chemical and physical characteristics, and the results that were obtained are reported below.

CHEMICAL AND PHYSICAL CHARACTERISTICS OF POLLOCK LIVER OILS

	Liver Oil from emaciated fish	Liver oil from plump fish
Specific Gravity at 25°C	0.9221	0.9217
Refractive Index at 20°C	1.4788	1.4788
Saponification value	187.3	187.3
Iodine Value	155.2	155.4
Acid Value	7.92	0.9833
Cold Test (Clouding Point)	12°C	6°C

In connection with the difference in the results of the cold test, it is of interest to note that when samples of these oils were allowed to stand for some months under identical laboratory conditions the precipitate of stearin from the liver oil obtained from emaciated pollock was more than twice as large as that from the oil obtained from the plump pollock.

Also there was a marked difference in the color of the liver oils obtained from the emaciated and plump pollock. The oil from the emaciated fish was of a pronounced reddish shade, while that from the plump fish was of a straw yellow color. A colorimetric analysis* of these oils by means of Lovibond glasses showed them to have the following composition.

	Yellow	Red
Liver oil from emaciated pollock.	35	55
Liver oil from plump pollock	35	5.4

FEEDING TESTS

The experimental diet, which consisted of casein 18%, peanut oil 22%, salt mixture 4%, cornstarch 28% and milk sugar 28%, was prepared from the same stock of material and in the same manner as the diet discussed in detail in an earlier publication.[2] This diet, which is free, or nearly so, from vitamines "A" and "B", was made adequate from the vitamine "B" standpoint by the daily addition of 0.2 gram of dried brewer's yeast to the diet of each animal. The pollock liver oil under test was added to the diet of the experimental animals in the same manner as previously discussed, viz., the amount of liver oil desired was dropped upon a pulverized yeast tablet, which was always eaten with great avidity. In view of the high vitamine "A" potency of fish liver oils, it was

* The author is indebted to Herbert S. Bailey of the Southern Cotton Oil Co. for the above colorimetric analysis.

necessary that only very small amounts of pollock liver oil should be administered, and this was accomplished by diluting the pollock liver oil with peanut oil. For this purpose twenty three parts of peanut oil from the same lot as that included as an ingredient of the experimental diet was thoroughly mixed with one part of pollock liver oil.

Albino rats were used as the experimental animals in the feeding tests reported below. All the experimental animals were developed in our breeding colony, and they were believed to be of quite uniform characterictics as compared with each other and as compared with experimental animals used in similar tests of the vitamine potency of a number of other fish oils which have been under investigation.

On referring to the growth charts, it will be noticed that the amount and rate of body increment for rats Nos. 37 and 38 is greater than that of the other experimental animals. It is believed that the long continued growth of these two experimental animals was possible through the storing of vitamine "A" in their bodies as a result of feeding of skimmed milk for a period between weaning and starting on the experimental diet. The other animals were started on the experimental diet very soon after weaning.

In order to make possible some estimation of the relative vitamine potency of different liver oils, the amount of pollock liver oil administered to the different experimental animals was varied. In those experiments with pollock liver oil obtained from emaciated fish, the amount of oil administered varied from approximately 2 mg. per day to approximately 7 mg. per day. In those experiments to determine the vitamine potency of pollock liver oil obtained from plump fish, the amount of oil administered varied from approximately 1 mg. per day to approximately 5 mg. per day. In each series of feeding tests it will be noticed that the animal receiving the smallest amount of pollock liver oil did not grow at as rapid a rate as those animals which received larger amounts.

In the first series of experiments animal No. 60, which received 3.4 mg. of pollock liver oil per day, appeared to recover from malnutrition at as rapid a rate as those animals which received larger amounts of the pollock liver oil, indicating that for this animal 3.4 mg. of this liver oil from emaciated pollock was sufficient to meet the body requirement for

vitamine "A". The same type of results was obtained in the second series of experiments. Rat No. 63 recovered from malnutrition at as rapid a rate as those animals which received in excess of 1.9 mg. of pollock liver oil per day. Consequently, from this series of experiments it would seem that [illegible] of this liver oil from plump pollock supplied sufficient vitamine "A" for the body needs of the experimental animal. While it is impossible to generalize very far on such limited data, it appears that the vitamine potency of pollock liver oil obtained from the plump fish was somewhat higher than that of the oil obtained from the emaciated pollock. Also comparing the results noted above for the vitamine potency of emaciated pollock with similar results previously reported for emaciated cod fish[1], it appears from this limited data that the potency of the pollock liver oils is slightly in excess of that of cod liver oil obtained from cod fish of similar physical condition. To provide additional data concerning the vitamine potency of fish liver oils, the comparative study of pollock and cod liver oils is being continued with oils from fish taken at different seasons of the year.

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QUANTITATIVE AND QUALITATIVE CHANGES IN THE ISLANDS OF LANGERHANS IN DIABETES MELLITUS.

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The first evidence of a possible etiologic relationship between lesions in the pancreas and diabetes mellitus was brought forward by V. Mering and Minkowski in 1889, when these investigators produced a rapidly fatal diabetes in dogs by total pancreatectomy. Several years later, Ssobolew and Schulze showed that ligation of the pancreatic ducts, a procedure which as they pointed out, resulted in the degeneration of the acinar tissue with no involvement of the islands, was not followed by glycosuria. The real significance of these experimental observations received little emphasis until Opie, in 1900, published his studies upon this subject. Opie emphasized particularly the rôle of the islands of Langerhans in the internal secretion of the pancreas, and to him belongs the credit for focusing the attention of investigators upon these structures in their relation to the pathology of human diabetes. A careful anatomical study of the pancreas in a number of autopsies was made with a view to a correlation of pancreatic lesions and glycosuria. It was found in a large percentage of cases of diabetes, the pancreas showed a fairly diffuse fibrosis, so-called chronic interacinar pancreatitis, with not only a reduction in the acinar tissue, but more or less sclerosis or hyalinization of the insular tissue as well; whereas examples of interlobular fibrosis were not in general associated with glycosuria except where the fibrosis was extensive with involvement of the insular tissue. In other words, the findings tended to show that the islands, and not the acinar tissue, were concerned in carbohydrate metabolism.

Following the publication of Opie's results, many investigators took up the study of the question in an endeavor to establish or disprove the so-called "island theory" of dia-

betes, and in reviewing the literature, one finds a number of contradictory reports.

Among those whose studies tend to support the island theory are Weichselbaum and Stangl, Ssobolew, Sauerbeck, Hoppe-Seyler, Cecil, MacCallum, Winternitz, Homans, and Allen, while among those obtaining negative findings are v. Hansemann, Major, and Herxheimer.

Brief reference will be made to the findings of these investigators in connection with the reports of our own observations which will be considered in two parts, first, quantitative, and second, qualitative changes of the islands of Langerhans in association with diabetes.

I. Quantitative Changes in the Islands of Langerhans.

Although a majority of the investigations of the pancreas in diabetes have been concerned with qualitative changes in the insular tissue there are a number of reports dealing with quantitative variations in the islands under both normal and pathological conditions. These reports may be divided roughly into two groups, (1) those based on general impressions obtained by examination of histological sections, and (2) those concerned with the actual enumeration of the islands. Among the first group are papers by Weichselbaum and Stangl, Ssobolew, Cecil, Winternitz, MacCallum, and Allen. Weichselbaum and Stangl made a careful study of the pancreas in 32 cases of diabetes and observed a reduction in the number of the islands in every case. No actual counts were made, the decrease being determined by comparison of the sections of the pancreas from non-diabetic cases. In the same year Ssobolew reported a diminution in the number of islands in thirteen out of fifteen cases. In four of the thirteen cases he claims the islands were entirely absent, an observation which has been questioned by subsequent workers. Cecil states that in about half of ninety cases of diabetes studied at autopsy the size of the pancreas or the number of islands was much less than normal and that in 20 cases there was marked diminution in the number of islands readily "recognizable by inspection of sections." Of thirty-four cases reported by Allen a reduction in the number of islands was judged to have been present in twenty, but the author was inclined to attach only

secondary importance to quantitative changes, regarding qualitative changes as of much greater significance. Several investigators including Reitman, Herxheimer, MacCallum, Cecil, and Winternitz, have observed examples of apparent hypertrophy of the islands in diabetes with probable increase in the actual number, the phenomenon being interpreted as a compensatory reaction, that is, a response to increased need, new islands being presumably formed out of acinar tissue or ducts.

As indicated above, the only published observations of attempts at a careful enumeration of the islands are found in the reports of Opie, Sauerbeck, and Heiberg.

Opie, in 10 non-diabetic cases, took a section each from the head, body, and tail of the pancreas and found an average of 23.4 islands per 50 square millimeters, while in 5 diabetic cases, by a similar method, he found an average of 21.8 islands per 50 square millimeters, from which he was led to conclude that there was no reduction in the islands in diabetes. Sauerbeck counted the islands in transverse sections of the pancreas from 12 non-diabetic cases, not more than 3 sections in each case being enumerated, and found an average of 135 islands per cross section, as against an average of 48 in 9 cases of diabetes. Similarly, Heiberg, in 48 non-diabetic cases, enumerated the islands in sections from the tail of the pancreas, the area counted being in each case 50 square millimeters. He studied 100 preparations in all, an average of approximately 2 sections to each case, and found that the majority contained from 76 to 150 islands and in none was the number less than 50. In 14 cases of diabetes on the other hand only 25 to 50 islands were found in most of the sections, and in no section were there more than 150 islands. From these studies Heiberg drew the following conclusion: "Where one has made 4 counts each from sections of the tail, and 3 of the sections give counts below 60 islands per 50 square millimeters, while the 4th section does not show over 100 islands per 50 square millimeters, the diagnosis of diabetes is incontestable."

It is obvious that much of the reported data relating to the number of islands cannot be accepted by reason of the fact that the methods employed are open to large errors. For example, when the great variation in the island content of different portions of the pancreas is taken into account, it is

evident that counts based upon only one or even several sections are unrealiable. To be sure, Heiberg uniformly took sections from the tail in both diabetic and non-diabetic cases, and Opie examined sections from the head, body, and tail in all of his cases, so that their results are of far more value than those of Sauerbeck, who, in 5 non-diabetic and 5 diabetic cases, took only one section in each case from various parts of the organ. But the invalidity of the findings obtained by any of these incomplete methods will appear from an examination of the figures in case 6 of our control series. The average number of islands in this case as determined by a count of 25 sections was 342. But we could select three sections, one each from head, body, and tail, that would give an average of 243, or 3 other sections from these same parts, that would show an average of 486, or practically *double the previous figure*. In other words, anything less than a thorough study of the organ is likely to give untrustworthy findings.

The present quantitative study is based upon an investigation of the pancreas in 12 cases of diabetes and of 12 control non-diabetic cases. The method pursued was an follows: The pancreas was removed as soon after death as possible, in most cases within six hours, and was weighed and cut transversely into sections from head to tail, each cut being made at one-half to one and one-half centimeter intervals. Particular attention was given to this point, since, as most investigators have observed, different portions of the organ show wide variations in the number of islands, which are most numerous in the tail and least numerous in the body. It is clear, therefore, that a preponderance in the number of sections taken from any one part of the organ would falsify the results. After sectioning, the tissue was fixed in Zenker's fluid for 12 hours. The blocks were then serially numbered, embedded in paraffin, and cut in the usual manner into sections varying from 6 to 8 micra in thickness. Hematoxylin and eosin stain was used in all cases, since a preliminary study showed that the differentiation between islands and acinar tissue was, in general, as clear with this routine stain as with any of the special stains tested. The total number of islands in each complete cross section was counted with the use of a low power objective and a mechanical stage. After a little practice with the method, the enumeration did not prove to be as laborious

as had been anticipated. Very small islands, some containing as few as 8 cells, were included in the counts. Islands which showed hyalinization were counted separately, so that the figures obtained afford an index of the qualitative as well as of the quantitative changes in the insular tissue. After counting the islands in all of the sections of a single pancreas, the average number of normal islands per cross section was easily computed by dividing the total count by the number of sections. The figures obtained for many of the sections were verified by a second count made several weeks later without reference to the original count. In no cases did the two counts differ by more than 10 per cent, indicating a relatively small margin of error.*

In the following tables the figures for the 12 non-diabetic and 12 diabetic cases are given, together with the age, weight, height, and autopsy findings. It will be noted that in the table of diabetic cases, pancreatic changes are omitted under the heading of "autopsy diagnosis," only the general findings being included, while the pancreatic changes are referred to under the heading of "note on pancreas".

Only those islands which are hyalinized are enumerated in a separate column. Those showing fibrosis, without hyalinization, are included in the count of normal islands.

In the 12 non-diabetic cases it is seen that the average number of normal islands per cross section of pancreas showed rather striking differences, the number ranging from 86.9 to 342.0. However, with a single exception, the number in each case is higher than that in any of the diabetic cases, among which the figures ranged from 46.5 to 95.4 per cross section. The average for the former group, 183.6 also contrasts strikingly with the average figures of 73.6 for the cases of diabetes. It is possible, of course, that in a larger series of cases, such marked differences might not be found.

* Reference should be made in this connection to a method of counting the islands through the use of vital stains, devised by Bensley. A weak solution of janus green or neutral red is injected into the pancreas through the aorta immediately after death. The islets being more deeply stained than the acinar tissue may be readily enumerated by means of a hand lens. The method has been used by Bensley to estimate the total number of islands in the guinea pig pancreas, and by Clark in studies upon the human gland. Both investigators found marked variations not only in the number of islands in different portions of the same organ, but also in the glands of different individuals of similar age. A serious objection to the general use of the method in the study of human material is the fact that very fresh tissue is necessary.

Diabetic Cases

Case No.	Aut. No.	Name	Age	Weight	Ht. in.	Aut. Diagnosis	Pancreas wt. grams	ACINAR CHANGES		INSULAR CHANGES				No. of microscopic sections	Total No. of isles in sections	No. of normal isles	No. of hyalinized isles.	Average No. of normal isles per section.
								Fibrosis	Necrosis	Atrophy	Hypertrophy	Fibrosis	Hemangiectases					
1	3	Mrs. L. S.	53	81	60.4	Fracture of femur.	60	+	—	+	—	50%	+	33	2275	2275	0	62.2
2	70	Mrs. F. H.	43	124	64.3	.....	80	+	—	—	+	60%	—	17	1155	1155	0	68.0
3	276	Mrs. M. B.	65	260	63.2	Acute tracheobronchitis; bronchopneumonia.	110	+ +	—	+	—	25%	—	25	2027	1654	373	66.1
4	294	Mr. F. H.	45	125	60	Bronchopneumonia.	110	+	—	—	—	10%	+	30	2759	2759	few	91.9
5	346	Mrs. A. G.	43	130	60	Breast abscess; septicemia.	— —	—	—	+	—	30%	—	10	1057	954	103	95.4
6	359	Mr. G. W.	44	102	63	Acute pancreatitis.	85	+	+	+	—	25%	—	13	1352	830	522	63.8
7	400	Mr. W. A.	55	162	69	Cellulitis of hand; septicemia.	72	+	+	—	—	10%	—	10	805	776	29	77.6
8	452	Mr. R. M.	65	120	—	Arteriosclerotic kidney.	90	—	+	+	—	—	—	21	1296	976	320	46.5
9	455	Miss J. W.	59	115	61	Cellulitis of hand; septicemia.	55	+	—	+	+	10%	—	15	1386	1386	0	92.4
10	481	Mr. G. P.	57	155	64	Multiple visceral abscesses.	125	+	—	—	—	—	—	5	386	356	12	71.2
11	586	Mrs. A. K.	59	116	65.6	Cerebral hemorrhage	105	+	—	—	—	—	—	14	3359	1301	2058	92.9
12	592	Mr. J. B.	61	94	64	Lobar pneumonia	50	+ +	—	+	—	—	—	16	831	766	6	47.9
																Average		73.6

Case No.	Aut. No.	Name	Age	Weight lb.	Ht. in.	Aut. Diagnosis	Pancreas wt. grams	ACINAR CHANGES		INSULAR CHANGES				No. of microscopic sections	Total No. of islets in sections	No. of normal islets	No. of hyalinized islets.	Average No. of normal islets per section.
								Fibrosis	Necrosis	Atrophy	Hypertrophy	Fibrosis	Hemangiectases					
1	18	Mr. M. C.	43	110	60	Chr. and acute mitral endocarditis.	101	—	+	—	—	10%	—	32	4860	4860	0	151.9
2	263	Mr. M. W.	46	105	78	Pernicious anemia	—	—	—	—	—	—	—	16	2275	2275	0	142.0
3	550	Mrs. M. H.	66	106	—	Carcinoma of rectum	65	+	—	—	—	—	—	21	1920	1825	95	86.9
4	551	Mr. C. S.	18	142	69.8	Acute arsenic poisoning	62.5	—	—	—	—	—	—	16	1805	1805	0	113.0
5	555	Mrs. A. D.	65	124	61	Pulmonary embolus.	60	+	—	20%	—	+	—	26	4316	4316	0	166.0
6	557	Mrs. M. S.	58	114	63	Arterioscelerotic kidney.	—	—	—	—	—	—	—	25	8555	8555	0	342.0
7	563	Mrs. B.	57	125	—	Cerebral hemorrhage	—	—	—	—	—	—	—	25	4829	4829	0	191.3
8	596	Mr. A. C.	72	67	55.2	Carcinoma of caecum.	59	—	—	—	—	—	—	21	3351	3351	0	159.6
9	607	Miss R. G.	31	194	66.9	Lobar pneumonia	81.5	—	—	—	—	—	—	14	3161	3161	0	225.8
10	609	Mr. J. F.	91	123	55.2	Senility	56	+	—	—	—	—	—	17	3408	3408	0	200.5
11	610	Miss E. C.	35	155	63.6	Chr. and acute diffuse nephritis.	55.5	+ +	—	—	—	—	—	15	2173	1956	217	130.4
12	612	Mrs. T. C.	66	150	68.4	Pernicious anemia	91	+	—	—	—	—	—	12	3504	3504	0	292.0
																Average		183.6

On the other hand, it is conceivable that the single non-diabetic case (No. 3) which was the only one in the series showing both a low island count, and hyalinization of the insular tissue, might have been a "potential" diabetic, that is, an individual with low carbohydrate tolerance. Unfortunately, the clinical record in this case contains no data bearing on this point. We know only that there were no symptoms suggestive of diabetes and that a routine urine examination showed no sugar.

II. Qualitative Changes in the Islands of Langerhans.

Beginning with Opie's work already referred to, there have been numerous studies of the pancreas in diabetes, and the majority of these as stated above have been concerned with qualitative changes in the islands. Since the subject has been well reviewed in the papers of several previous workers reference will be made here only to the more noteworthy contributions.

Weichselbaum and Stangl, in addition to a decrease in size and number of islands observed in their study of 32 cases, degenerative changes, chiefly hydropic degeneration and fibrosis in many of the islands. Hemorrhages were seen in 3 of the cases. Ssobolew also noted hydropic degeneration in 2 out of 15 cases. Hoppe-Seyler in an attempt to correlate sclerotic changes in the pancreas with glycosuria, investigated 18 cases of generalized arteriosclerosis, in all of which there was more or less fibrosis of the pancreas. Nine of the cases were diabetics, and 9 were non-diabetic. In the diabetic group hyalinization of the islands was found in 2, atrophy in 4, marked fibrosis in 3, slight fibrosis in 2, and absence of islands in 1. In the non-diabetic group the island changes were much less marked, there being only a slight atrophy and fibrosis in a few of the cases. Hoppe-Seyler concluded that the degree of qualitative change in the islands corresponded fairly closely with the intensity of the diabetes. By far the largest series of cases hitherto studied by a single observer is that of Cecil. The series included 90 cases of diabetes. Cecil found definite changes in the islands in 79, the commonest lesion being fibrosis which was present in 76, while hyaline degeneration was noted in 27. Unfortunately, Cecil's very significant findings

were not controlled by a simultaneous study of non-diabetic material. More recently Allen in studies upon both experimental diabetes in dogs and the spontaneous disease in man has emphasized the presence of hydropic change in the island cells which he regards as a lesion, pathognomonic of active diabetes. The change is interpreted as a "specific diabetic phenomenon produced solely by overstrain of the function of the cells by diets in excess of the weakened assimilative power." While Allen observed the change regularly in the pancreas of dogs with fatal diabetes, he was able to positively identify it in only three out of 21 cases of human diabetes. He states, however, that the change was "evidently present in 5 others where it was blurred by post mortem changes." The frequent absence of the lesion in human material Allen believes can be accounted for, first, by the imperfect preservation of the pancreas after death, and secondly, by the fact that death occurs in many instances not as the result of the diabetes per se, but from some associated condition such as inanition or infection.

The above comprises some of the strongest evidence in favor of the insular theory, and upon analysis it appears fairly convincing. On the other hand, there is some evidence against the theory, not nearly so abundant, and, on the whole, less convincing.

In spite of a very careful study by v. Hansemann of 34 cases of diabetes, none was encountered where the islands were missing, and although in some of the cases in which the pancreas showed his so-called "granular atrophy" with great destruction of the parenchyma, the islands were few in number, the latter showed no pathological change. In the entire series studied, only 8 cases were encountered where the islands were hyalinized, and in all cases where the islands were altered changes in the acinar tissue were also found. It is significant, however, that v. Hansemann did not observe a single instance of hyalinization of the islands in non-diabetic cases. Major studied the pancreas in 13 cases of diabetes and in 35 non-diabetic. Seven of the diabetic cases showed no alteration whatever of the islands; while in the five cases in which there was some hyalinization and fibrosis of the insular tissue, normal islands were numerous and the fibrosis of the affected islands was no more marked than in some of the control cases.

It is a noteworthy fact that Major found in the non-diabetics 26 instances of fibrosis of the acinar tissue, so-called chronic pancreatitis,—out of a total of 35 cases, or 75%, a higher incidence of such change than other workers have reported. In our series, as will be brought out later, the incidence was approximately 30% in cases over twenty years old, and considerably lower in younger individuals. In a series of 20 cases of diabetes Herxheimer found the islands normal in two-thirds of the cases, and in no case were they greatly altered. In a later article he claims to have observed the development of islands from acini, and concludes that the cells of both the acini and islands are concerned with carbohydrate metabolism.

The material for our studies has consisted first of all of 24 cases in which multiple sections of the pancreas were made for the purpose of enumerating the islands. Twelve of the cases were diabetic, with 12 controls. In addition sections of the pancreas were examined from 168 routine autopsies on non-diabetic cases in which the autopsy was performed within 4 hours after death, but since in 60 of these there was evidence of well marked autolysis, the material was discarded, leaving one of these cases, as was mentioned in connection with the findings are discussed separately, there are altogether 120 cases, with 12 diabetics and 107 controls.

The findings in the 24 cases in which the pancreas was studied exhaustively with sections from serial blocks through the entire organ, will be considered first. These cases, as explained above, were studied primarily with a view to quantitative estimation of the islands, a study which gives unusual opportunity for the recognition of qualitative changes. In the 12 diabetics hyaline islands were observed in 9, fibrosis of the islands in 9, hydropic change in one, and hemangiectases in 2. In every case the islands were more or less affected. In several cases the hyalinization was very striking (Figs. 2 and 3). In the 12 controls in which the same thorough study was made, only two showed hyaline islands. In one of these (Case 3) the hyalinization was quite marked but involved only 95 out of 1920 islands counted, while in the other instance (Case 11) there was slight hyalinization in 217 out of 2173 islands. In both these cases, as was mentioned in connection with the quantitative studies, the total number of islands was below normal. In the case of hemochromatosis there was very little

hyalinization or fibrosis of the islands but the cells everywhere showed more or less pigment deposition which may very well have interfered with cell function. Since hemochromatosis is a disease *sui generis,* we are purposely not including it in the series.

As regards the changes in the acinar tissue the following is a summary of the findings. In the diabetic group 10 cases showed well marked fibrosis, generally mixed in character, inter—and intra—lobular; one, acute suppurative pancreatitis, and 3, fat necroses. In the non-diabetic group 6 of the 12 cases showed fibrosis which, however, was generally very much less marked than in the cases of the diabetic group.

Of the 95 control cases in which the pancreas was less thoroughly studied there were 24 instances of fibrosis, a much smaller percentage, it will be noted, than in Major's series of non-diabetic cases referred to above. Analysis of the cases shows that 21 of these 24 instances of fibrosis occurred in 65 cases of patients more than 20 years old, there being only 3 examples of fibrosis in cases dying under 20. Lipomatosis was present to a greater or less degree in both the diabetic and non-diabetic groups, and since the fatty replacement of the acinar tissue is so commonly seen in association with general adiposity we have not considered the change of sufficient significance to warrant its discussion.

A very careful study of all cases was made with respect to hydropic changes in the islands emphasized recently by Allen and to which reference has been made earlier in this paper. In only one instance was the lesion sufficiently definite to make its recognition by us beyond doubt. (Figs. 5 and 6) This was in case 12 of the diabetic series. The tissue had been fixed within 2 hours after death and was obviously better preserved than in the majority of cases of both diabetics and controls. One other case of the diabetic series, Case 9, showed occasional hydropic cells in the islands, but since a similar appearance was noted in several non-diabetic cases no significance was attached to the findings. In some instances a combination of hydropic change and hyalinization was observed. (Fig. 7, Case 12).

In brief, we feel that the significance of this lesion, so-called hydropic degeneration, has yet to be determined. It may be true, as Allen maintains, that for the recognition of the change

the tissue must be fixed immediately after death. It is, however, difficult to understand how cells, the cytoplasm of which is so strikingly vacuolated as in Case 12, could lose their vacuolated character and present the picture of a well stained cytoplasm as is observed in a number of the other cases.

Hypertrophy of the islands was noted in two diabetics. In one of these there was a large adenomatous nodule of insular tissue in the head of the organ. (Fig 8). Atrophy of the islands was seen in seven cases. (Fig 4).

Summary.

A thorough study was made of all parts of the pancreas in 12 cases of diabetes and 12 controls of similar age, and a less thorough study of 95 routine autopsies of non-diabetics. Both quantitative and qualitative differences were found in the diabetic and non-diabetic groups. In the diabetic group an enumeration of the islands in sections from serial blocks of tissue through the entire organ showed a marked reduction in the amount of insular tissue. The average number of islands per cross section was 73.6 as compared with 183.6 in the controls. In only one non-diabetic case was the count as low as the highest figure in the diabetic group.

Every case of diabetes showed more or less qualitative changes in the islands, chiefly hyalinization and fibrosis, the latter lesion being quite widespread in some cases. Hyalinization of the islands was seen in only two cases of the non-diabetic group, and in these it was not so marked as in the majority of the diabetic cases.

Definite hydropic degeneration of the islands was observed in only one of the diabetic cases and in none of the controls, but it is possible that the tissue in most cases was not fixed sufficiently early after death for a satisfactory study of this lesion. Changes involving the acinar tissue, particularly interacinar and interlobular fibrosis were seen in both series but were more marked in the diabetic cases.

From this study it is concluded that both quantitative and qualitative changes are operative in leading to a functional insufficiency of the insular tissue as manifested by clinical diabetes.

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Clinical Abstracts of Diabetic Cases *

Case No. 1.—Mrs. L. S., aged 53.

The immediate cause of patient's admission to the hospital was an injury resulting from a blow by a swinging door which threw her down a stone step. Further questioning revealed the fact that she suffered from polyuria, nocturia (4 times), and polydipsia for many years. She was told by a doctor she had diabetes. Whether she received or adhered to any treatment could not be learned.

Examination showed a fracture of the neck of the humerus and femur. Repeated examination of the urine showed sugar. The course in the hospital was afebrile. She died very suddenly three weeks after entrance.

Clinical Diagnosis.—Diabetes mellitus (severe); fracture of neck of left femur and humerus.

Case No. 2.—Mrs. F. H., aged 43.

The patient was admitted to the hospital in an unconscious state. Five years ago she had a "thyroid operation." Otherwise there was nothing noteworthy in her past history. The patient had not been feeling as well as usual during the winter and spring preceding admission. She had been very thirsty and had to urinate at least five times every night. In one twenty-four hour period she passed 14 quarts of urine. On the morning of admission she got up with a headache and two hours later became unconscious. She had no convulsions.

Examination showed the following. Respirations, 30 per minute and deep; temperature, 102°F. Heart, lungs, and abdomen, negative. Extremities, edematous. Blood pressure, 70 systolic. Leukocyte count, 26,000 Urine, pale, clear, with 5 per cent. sugar (polariscope), acetone, and diacetic acid. The day after admission the temperature rose to 104°F and the pulse to 140 per minute. Death occurred quite suddenly.

Clinical Diagnosis.—Diabetes mellitus; acidosis; coma.

Case No. 3.—Mrs. M. B., aged 65.

The patient entered the hospital because of a sudden attack of breathlessness. She has always been subject to sore throats and earaches, and for the past ten years her legs have swollen quite frequently. She also has had recurring attacks of eczema of the lower extremities. There has been nocturia for some time. Her acute illness started the night before entrance with a chill which continued well on into the morning

* The author is indebted to the medical service of the New Haven Hospital for the clinical data incorporated.

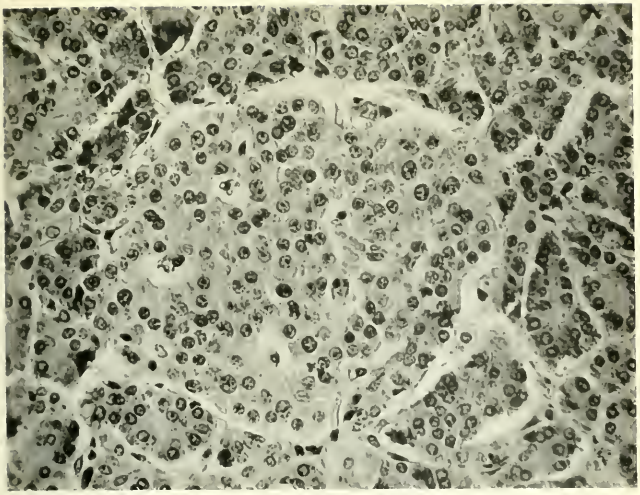


FIGURE I.

Normal island of Langerhans. Case 2.
x 375.

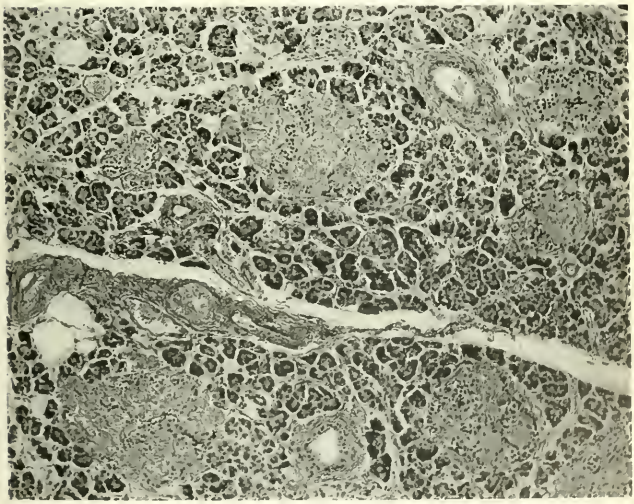


FIGURE II.

A group of five hyalinized islands. Case 11.
x 100

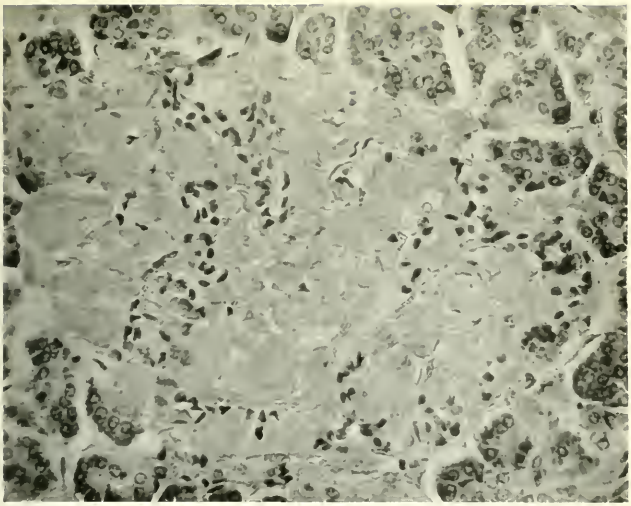


FIGURE III.

High magnification of one of the hyalinized islands shown in Fig. II.
x 375

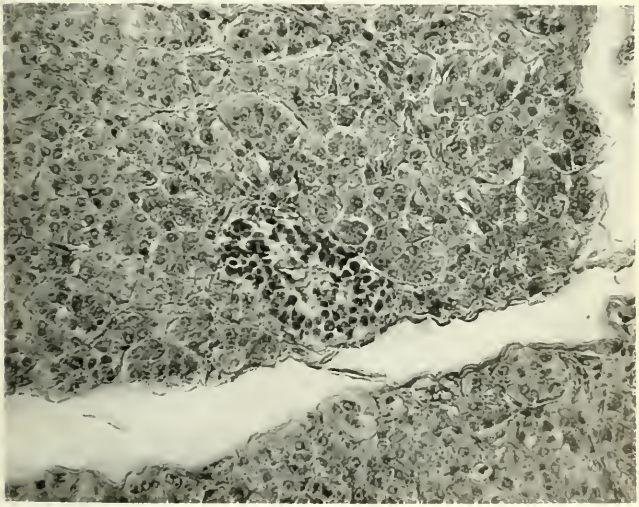


FIGURE IV.

Atrophic island the cells of which show pycnotic nuclei and scanty cytoplasm. Case 12.
x 375

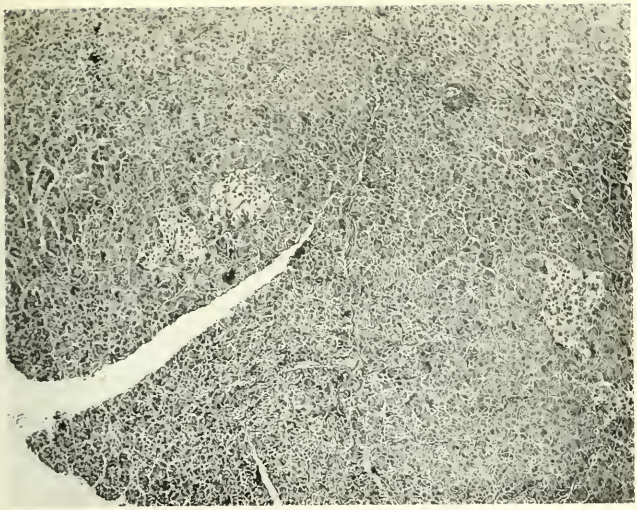


FIGURE V.

Three hydropic islands the nuclei of which are widely separated by the abundant vaculated cytoplasm of the cells. Case 12.
x 100

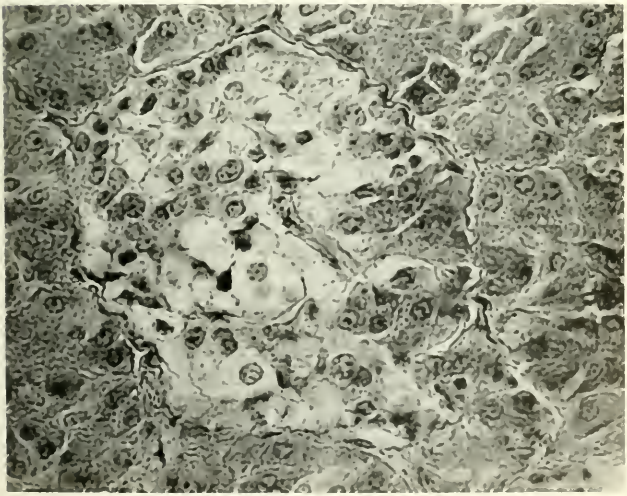


FIGURE VI.

A hydropic island under higher magnification.
x 650

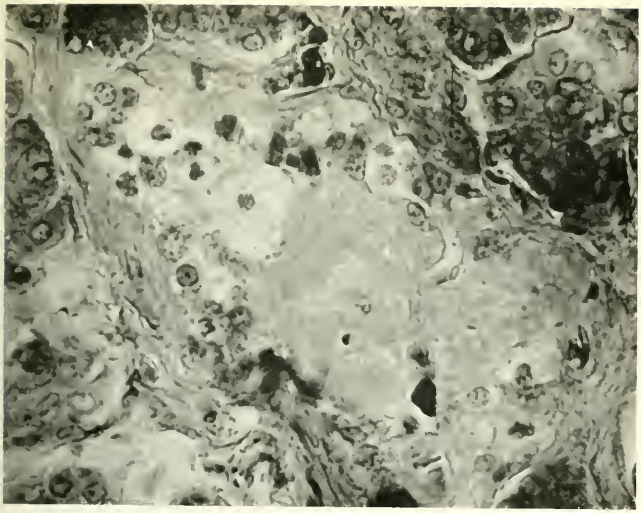


FIGURE VII.

An island show both hyalinization and vacuolization. Case 12.
x 650

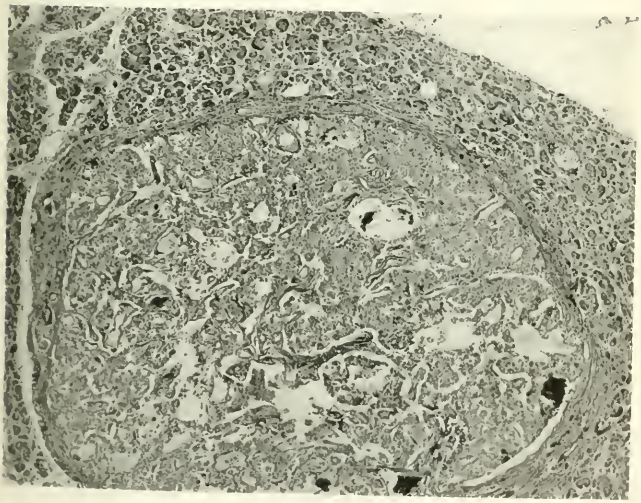


FIGURE VIII.

Adenomatous hyperplasia of island tissue, large nodule in head of pancreas. Case 10.
x 50

of the day of admission. She further began to experience difficulty in getting her breath and felt faint.

The findings of note on examination were obesity, dyspnea, irregular pulse with extra systoles, cardiac dulness increased to both right and left, systolic murmurs both at apex and over aortic areas, dulness and moist rales at the bases of both lungs, enlarged firm liver, pendant edema, erysipelatous area over left leg. Temperature, 102°F. Blood showed polynuclear leukocytosis of 32,000. Blood pressure was 160/75. Blood urea, 36; blood nitrogen, 50; blood sugar, 167 mg. per cent. Urine showed albumin, hyaline casts, a few red and white blood cells, and a trace of acetone but no sugar. The patient's condition grew progressively worse and she died four days after admission.

Clinical Diagnosis.—Chronic myocarditis; myocardial insufficiency; erysipelas of left leg; obesity.

Case No. 4.—Mr. F. H., aged 45.

The immediate cause of patient's application for admission to the hospital was pain in the left side. Five days before entrance he felt feverish, had a severe chill, and shortly began to have difficulty in breathing and developed a cough. Pain in the side was exaggerated by deep inspiration and had caused him much discomfort. He felt weak and depressed on entrance.

Examination showed slight cyanosis, rapid deep respiration; diminished expansion on left side; marked dulness from left scapula down to base with a loud friction rub. Expiration was harsh and prolonged and many moist rales were heard. Leukocyte count was 22,000. Temperature ranged from 99.5° to 103°F; pulse from 110 to 160; respirations from 40 to 60. On the day after entrance the breath was laden with acetone and the breathing was air hunger in type. The patient became more and more cyanotic, gradually went into coma and died two days after admission. The urine showed 33.5 per cent sugar (polariscope), acetone, and diacetic acid. Blood sugar was 570 mg. per cent. (The patient's father died of diabetes at the age of 80 years.)

Clinical Diagnosis.—Pneumonia; pleurisy; diabetes mellitus.

Case No. 5.—Mrs. A. G., aged 43.

The patient had never been ill until 2 months before admission and then she began to feel "run down" and developed a breast abscess which was incised under ether anesthesia on the morning of admission. Following this she became drowsy and toward evening went into coma and was sent into the hospital in that condition. On entrance respiration was of the air hunger type with an acetone odor to the breath.

Physical examination was essentially negative. Red blood cells, 3,500,000; white blood cells, 38,500. The urine showed albumin, sugar 3.12 per cent (polariscope), acetone, and diacetic acid. Blood pressure was 70 systolic. The patient became rapidly weaker and died the day after admission.

Clinical Diagnosis.—Diabetes mellitus; acidosis; incised breast abscess; chronic nephritis; septicemia.

Case No. 6.—Mr. G. W., aged 44.

Three years before admission the patient began to be troubled with polyuria, polydipsia, polyphagia, and weakness. He consulted a physician who told him he had diabetes and prescribed a diet. The patient adhered to the diet for only a short time. In addition to the above symptoms he has felt tired and sluggish and has lost 17 lbs. in weight. One week previous to admission he had 19 teeth extracted and since then has felt very weak. Two days before admission he became drowsy and lapsed into coma in which condition he was admitted.

Examination showed patient emaciated, breathing labored and deep, and breath laden with acetone. There was a little pus oozing from the gum edges. The chest, abdomen, and extremities were normal. His condition grew rapidly worse and he died the day after admission. Temperature was subnormal. No urine was obtained by catheterization. Blood sugar was 840 mg. per 100 cc. of blood.

Clinical Diagnosis.—Diabetes mellitus; acidosis.

Cases No. 7.—Mr. W. A., aged 55.

The patient's father died of diabetes. Fifteen years ago the patient began to develop insatiable thirst and appetite and passed large quantities of urine. He consulted a doctor who told him he had diabetes and put him on a diet. The patient has not adhered to the diet, and during the past fifteen years has lost 80 pounds in weight. Two weeks before admission he developed a cellulitis of his hand which was incised. This had been getting worse and was the immediate cause of admission.

Examination on entrance was essentially negative except for the left hand which showed a through and through incision between 4th and 5th metacarpals from which thick creamy pus exuded. The temperature ranged from 99°F to 104°F. Death occurred 12 days after admission. Blood sugar varied from 250 mg. to 384 mg. per cent. Sugar in urine varied from 1.4 per cent to 1.75 (polariscope). Urine also contained acetone and diacetic acid.

Clinical Diagnosis.—Diabetes mellitus; cellulitis of left hand; septicemia.

Case No. 8.—Mr. R. M., aged 65.

Four years before admission the patient had acute articular rheumatism of six weeks duration. He was admitted to the hospital where it was found he had diabetes and nephritis. He was put on a milk diet and was discharged improved a few weeks after entrance. His present admission was initiated by an acute respiratory infection of one week's duration followed 2 days before admission by delirium and drowsiness.

Examination showed him comatose with breathing of Cheynes-Stokes type suggesting air hunger. There was dulness and moist rales in the interscapular region. Temperature was 104° F, pulse 110 per minute. His condition became rapidly worse and he died 6 days after admission. Leukocytes were 40,000; hemoglobin, 60 per cent. The urine showed

a trace of acetone and diacetic acid but no sugar. Blood sugar was 66 mg. per cent. The urine contained 1 gram of albumin and gave a positive Guaiac reaction.

Clinical Diagnosis.—Chronic diffuse nephrilis; uremia; acidosis; lobar pneumonia.

Case No. 9.—Miss J. W., aged 59.

The patient's mother died of kidney trouble and diabetes. Seven years before admission the patient had a "shock" with left sided paralysis which cleared up in a few days. She had a similar "shock" six months previous to entrance which cleared up slowly and left her left arm weak. Five weeks before admission she began to vomit after meals and consulted a physician who told her she had diabetes. Since then she has been thirsty and has had frequency and polyuria. She has also had dull ache in the left side of her back for 4 weeks.

On admission the patient was comatose. Temperature was 104°F, pulse 140 per minute, respiration 60 per minute. There was an irregular superficial mass in the left side of the abdomen. The right hand was swollen and inflamed and also the left hand with a healed sinus over it. Leukocytes were 26,000 with 96 per cent polynuclears. Blood culture showed Staphylococcus aureus. Blood sugar was 666 mg. per 100 cc. of blood. Urine contained 0.73 per cent sugar (polariscope). The patient died the day after admission.

Clinical Diagnosis.—Diabetes mellitus; acidosis; uremia; septicemia; perirenal abscess; bronchopneumonia.

Case No. 10.—Mr. G. P., aged 57.

The mother and father of the patient both died of diabetes. The patient was treated for diabetes 17 years ago although he had no symptoms at that time. He has not adhered to diet and has eaten and drunk heartily. He has had polyuria. During the past two years he has had ulcers on his leg and has noticed that slight abrasions elsewhere healed indolently. A week before entrance he had a small pimple on the left cheek which grew in size and was incised by a physician. The infection spread until the whole right side of the face was involved.

Examination showed the left cheek swollen with a discharging sinus in its center. The skin was red and hot. Leukocytes were 15,000 with 84 per cent polynuclears. Temperature ranged from 100° to 102° F. Blood pressure was 185/100. Blood urea, 16; blood nitrogen, 33; blood sugar varied from 333 mg. to 435 mg. per cent. Urine showed 2.25% to 5.15% sugar, acetone and diacetic acid. On the 11th day after entrance, the patient became comatose and died.

Clinical Diagnosis.—Diabetes mellitus (severe); carbuncle of face.

Case No. 11.—Mrs. A. K., aged 59.

On the morning of admission the patient was found lying on the floor in an unconscious condition. All that could be learned was that three years previously a physician found sugar in her urine and told her that she had diabetes. She had always had a voracious appetite,

had been troubled with nocturia (twice), and noted that small cuts became easily infected and healed very reluctantly.

On admission the patient was comatose and the entire right side showed a flaccid paralysis. The urine gave a strongly positive reaction for sugar and the blood contained 211 mg. of sugar per 100 cc. Two days after admission signs of pneumonia appeared in the chest with corresponding rise in temperature, pulse, and respiration. During the next few days the pneumonic process became more marked and the patiend finally succumbed seven days after her admission.

Clinical Diagnosis.—Diabetes mellitus; hypertension; generalized arteriosclerosis; cerebral hemorrhage; bronchopneumonia.

Case No. 12.—Mr. J. B., aged 61.

The patient's illness extended over a period of 4 months preceding his first admission to the hospital during which time his chief symptoms were excessive thirst, polyuria, pruritus, and weakness which was marked enough to prevent him from working. Although general physical examination on admission was negative, the urine contained 3.8% sugar and the blood sugar was 434 mg. per cent. Starvation of 4 days duration resulted in cessation of glycosuria and three weeks after entrance, the blood sugar had fallen to 166.6 mg. per cent. The patient was discharged sugar free after 4 weeks stay in the hospital. Following discharge he failed to adhere strictly to prescribed diet and he lost weight. The old weakness returned 5 months after he left the hospital, and he promptly applied for readmission.

On readmission, the patient was slightly emaciated and there was an acetone odor to the breath, the blood sugar was 344 mg. per cent, and the urine contained large amounts of sugar. Shortly after entrance signs of pneumonia appeared in the right lung with concomitant rise of vital signs and death occurred on the third day after admission and 10 months after the onset of the patient's illness.

Clinical Diagnosis.—Diabetes mellitus; lobar pneumonia.

EFFECTS OF INSULIN ON DIABETIC DOGS.

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With the approval of the Eli Lilly Company, small quantities of the insulin (iletin, Lilly) kindly supplied by them to this Institute were used for certain animal experimental problems, even in the early period when the total supply of this extract was very limited. Because of this limitation, the observations made were only of a preliminary character, but the results in each instance were definite enough to permit conclusions.

1. Total Pancreatectomy.

Banting and Best[1] described the prolongation of life of totally depancreatized dogs, for periods up to 70 days in the longest instance, by means of injections of their earlier pancreatic extracts, which contained appreciable quantities of protein and other substances. These animals healed their wounds readily without infection, showed glycosuria, weakness and other typical symptoms without injections and a prompt clearing of all these symptoms with injections, and gradually emaciated to a point of fatal cachexia apparently because of digestive disturbance alone, due to lack of the external secretion of the pancreas. It seemed desirable to determine first whether the more highly purified preparation of the Lilly Company would duplicate these results.

Dog No. 89, a female brindle bull terrier, very weak and emaciated at a weight of 9 kg., was chosen for the special purpose of a test under adverse conditions. After total pancreatectomy at 7 P.M., subcutaneous insulin injections were begun in the attempt to prevent glycosuria and favor wound healing. The dosage necessary was entirely unknown, but was assumed to be rather large in comparison with the amount found necessary by Macleod[1] and co-workers to influence the blood sugar of normal rabbits. Accordingly 2 Lilly units of

iletin were injected at 9 P. M., and 2 more at 12 midnight. At 7:45 the following morning the animal appeared well except for noticeable weakness, and had passed no urine. Without taking a blood sample, another subcutaneous injection of 2 units was given at this time on the mistaken assumption that the weakness was due to uncontrolled diabetes. At 11 A. M. the dog was found almost dead with typical symptoms of hypoglycemic collapse. The plasma sugar at this time was 0.033 per cent.

The animal in this state was cold, barely conscious, and unable to stand. Another symptom, which on later occasions was found to be an early signal of impending collapse in this animal, was profuse salivation, equal to the effect of direct stimulation of the chorda tympani in normal dogs. Under observation the dog lapsed rapidly into profound unconsciousness, with relaxed muscles, feeble heart and gasping respiration. This coma was interrupted by occasional violent generalized convulsions, accompanied by loud cries and by involuntary voiding of urine and feces. During the quieter intervals there were sometimes general muscular tremors accompanying respiration, beginning with inspiration and ceasing at the close of expiration.

Intravenous injections of levulose were given as follows: 11 A.M., 5 gm.; 11:20 A.M., 3 gm.; 12:30 P.M., 12 gm. The first injection produced striking benefit. By 12 noon all symptoms except weakness had cleared up, though the plasma sugar was only 0.037 per cent. It may be noted that on November 19 this animal went into collapse with plasma sugar of 0.045 per cent., the same figure found by Macleod in rabbits; the exact level of blood sugar, therefore, appears to be not the sole determining factor. Though levulose appeared to be a sufficient antidote, 20 gm. glucose was given by stomach tube at 1 P.M. By 2 P.M. the animal was completely restored, and at 50 gm. of lean meat. At 7.30 P.M. the plasma sugar was 0.063 per cent.

The dog was unable to digest fat, which caused copious diarrhea. As the most easily digestible diet, a finely ground hash of bread and cooked meat moistened with hot soup was given as a routine, and milk was given in addition as a drink.

Bulky diarrhea was the rule nevertheless. After large feedings the dog sometimes vomited and immediately ate the vomitus. Owing to the frequent contaminations with vomitus and feces, only qualitative tests of the urine were performed, and quantitative analyses were limited to the blood. Table 1 shows the observations made.*

On the third day, it is seen that glycosuria remained absent with only one dose of 2 units of insulin at 9 A. M., and the plasma sugar at 1 P. M. was only 0.088 per cent; but by the following morning heavy glycosuria was present. Milk was given at this time, and a full feeding of bread and milk at 2 P.M.; nevertheless, 6 units of insulin caused collapse, from which, however, the animal was able gradually to recover without sugar injections.

The dosage of 2 units on the following (fifth) day was inadequate to control hyperglycemia and glycosuria. The same was true of the dosage of 5 units on the sixth day, when given in the form of 1 unit doses spaced out in the attempt to control the sugar uniformly throughout the 24 hours. Later experience gave the impression that 6 units per day was the ideal dosage, when spread out in the form of 1 unit every four hours. On the 7th day this controlled glycosuria but not hyperglycemia. On the 12th day low plasma sugars were thus maintained and the animal was in excellent condition, but the feeding of 50 gm. glucose at 9 P. M. produced heavy glycosuria and hyperglycemia. It may be of interest for human treatment, therefore, that in a totally depancreatized dog the identical dosage of insulin gave different results according to the plan of administration; when crowed into a period of five hours it produced hypoglycemic collapse, even though the entire diet for the day was given within this period, and by 8 o'clock the following morning faint glycosuria had returned; but distribution throughout the 24 hours maintained good health without glycosuria and with a fairly equable plasma sugar curve.

* The analytical methods used in this work were as follows: urinary and plasma sugar, Benedict; urinary and plasma total acetone bodies, and plasma bicarbonate, Van Slyke; plasma chlorides, Whitehorn; urea, urease; creatinin, Folin; phosphates, Bell and Doisy.

TABLE 1.

Dog No. 89.

Insulin Treatment after Total Pancreatectomy.

Day of Experiment	Hour	Units Insulin	Plasma Sugar	Glycosuria	REMARKS
1	9: P. M	2			
	12 Mid.	2			
2	7:45 A. M.	2			Weakened condition.
	11: A. M.		.033		Typical collapse. Intravenous levulose and glucose.
	12:		.037		
	2: P. M.				Great clinical improvement. Eats 50 gm. lean meat.
	7:30		.063		Marked improvement.
3	9: A. M.	2		negative	
	1: P. M.			negative	
	4:		.088		
4	9: A. M.	2		heavy	Given milk.
	12:	2		moderate	
	2: P. M.	2			Bread and milk.
	5:30 P. M.		.045		In typical collapse.
	7:				Clinical improvement.
5	8: A. M.			faint	Milk.
	9:30	1			
	5: P. M.		.206	moderate	
	7:	1			
6	9: A. M.	1		heavy	Faint acetonuria. Condition good.
	1: P. M.	1			
	4:30			heavy	Very lively.
	6:	1			
	8:		.283		Very good condition.
	9:	1			
	11:	1			
7	5: A. M.	1			
	9:	1		faint	Acetone negative. 80 gm. bread.
	10:		.263		
	11:		.217	faint	
	12:		.288		
	1: P. M.	1	.263		
	2:		.250		
	3:		.189		
	4:		.182		
	5:	1	.223		
	9:	1			
	12:	1			
8	5: A. M.	1			
	9:	1			
	11:30			negative	Large meal of hash.

TABLE I. *(Continued)*

Day of Experiment	Hour	Units Insulin	Plasma Sugar	Glycosuria	REMARKS
	1: P. M.	1	.234		Stitches removed. Hash given.
	2:				Hash.
	5:		.270	negative	Marked improvement.
	9:	1			
9	1: A. M.	1			
	5:	1			
	9:	1	.146	negative	
	1: P. M.	1			Hash given.
	5:	1	.120	negative	Hash.
	9:	1			
10	1: A. M.	1			
	5:	1			
	9:	1	.148	negative	
	12:30	1		negative	
	4:30 P. M.	1		negative	Hash.
	9:	1			
11	1: A. M.	1			
	5:	1			
	9:	1	.206	negative	
	1: P. M.	1		very faint	Hash.
	5:	1			
	9:	1		very faint	
12	1: A. M.	1			
	5:	1			
	9:	1	.125	negative	Excellent condition.
	10:		.067		
	11:		.069		
	12:		.078		
	1: P. M.	1	.130		
	2:		.078		Large meal.
	3:		.091		
	4:		.066		
	5:	1	.123	negative	
	9:				50 grams glucose.
13	9: A. M.		.469	heavy	
	1: P. M.				200 cc. milk.
	1:30		.518		
	4:		.789		Small amount of unstandardized insulin.
	4:30		.833		
	5:		.789		
	6:		.750		
	7:	1			
	8:30				Crackers and soup.
	9:	1			
14	1: A. M.	1			
	5:	1			
	8:30		.272	heavy	
	9:30	1			
	10:15		.283		
	12:10		.131		

TABLE I. *(Continued)*

Day of Experiment	Hour	Units Insulin	Plasma Sugar	Glycosuria	REMARKS
	1: P. M.		.162		400 cc. milk, 200 gm. bread.
	2:		.254		
	3:		.500		
	3:30		.526		
	4:10		.536		
	4:15				Small amount of unstandardized insulin.
	5:15		.518		
	5:45		.544		
	6:45		.446		
	11:		.600		
	11:30	2			Large meal.
15	5: A. M.	1			
	9:	1		faint	Large meal.
16	5: A. M.	1			
	8:45	1		heavy	
	1: P. M.		.209		
	1:30			very faint	Not so active.
	2:		.250		300 cc. milk. Bread refused. Dog weaker.
	3:		.341		
	4:		.429		
	5:		.544		
	6:		.600		
	7:		.638		
	9:		.668		
	10:		.668		
	10:45		.714		
17	9: A. M.		.732	heavy	
	9:45	1			
	10:30	2			
	1: P. M.	1			
	2:				50 gm. glucose.
	6:	1			
	7:45	1		heavy	
18	1: A. M.	1			
	5:	1			
	9:	1			
	2: P. M.	1		negative	50 gm. glucose.
	7:	1		faint	Returning liveliness. Hungry.
	9:30	1			
19	1: A. M.	1			
	5:	1			
	9:	1		negative	
	2: P. M.	1			
	6:	1		negative	Very good condition.
20	1: A. M.	1			
	5:	1			
	9:	1		negative	
	2: P. M.	1			50 gm. glucose.

TABLE I. *(Continued)*

Day of Experiment	Hour	Units Insulin	Plasma Sugar	Glycosuria	REMARKS
	5:30	1			
21	12: M.			heavy	
	1: P. M.	1			Crackers given.
	5:	1			50 gm. glucose.
22					6 units of insulin daily.
24	8:30 A. M.			negative	
27	9: A. M.				12 units of supposedly worthless insulin given.
	11:				Typical collapse. 5 gm. levulose intravenously. 15 gm. glucose by stomach tube. Recovery.
	12: M.				Typical collapse. 50 gm. glucose by stomach tube. 15 gm. glucose intravenously. Recovery.
	12:45				Tremors; 50 gm. glucose by stomach tube.
30					Animal found dead.

The fixed regularity of dosage was often interrupted by incidental conditions, especially lack of insulin. On the whole, the sugar was kept under control except for brief intervals which showed how promptly and heavily it would return in the absence of insulin dosage. It was considered especially important that the operative wound in the abdomen had healed very promptly, without the slightest tendency to delay or suppuration, in sharp contrast to the occurrences in any totally depancreatized dog heretofore known. The animal developed several small abrasions and ulcers over the joints, as commonly happens in cachexia, but these showed a tendency to heal rather than to burrow and perforate.

It was even more remarkable that this animal, which had been delivered to the laboratory in the weak and emaciated condition mentioned, apparently as the result of a homeless life in the streets, in the period of one or two weeks following pancreatectomy attained a condition of distinctly greater strength and liveliness than before operation. Omission of insulin, even for less than a day, was followed not only by gly-

cosuria but also by the typical lassitude and asthenia of a totally depancreatized animal, and these symptoms were quickly and completely removed by insulin injections.

On the whole, flesh and strength were gradually lost owing to inadequate digestion. No other factor was present as far as this experiment could reveal. The final weight was 8.4 kg., i.e., an apparent loss of only 0.6 kg. The smallness of the change was explained by the fact that the initial weight consisted chiefly of skeleton and shrunken muscles. A very marked further wasting of the muscles occurred, but was largely balanced by the enormous quantities of food with which the animal kept the abdomen distended. Death occurred on the thirtieth day after operation. It was hastened by the overdose of insulin given by mistake three days previously, from which the animal never fully recovered, but the weakness was so extreme that life could not have been prolonged more than a day or two further.

Autopsy showed the body to be practically free from visible fat. No vestiges of pancreatic tissue could be found in a careful gross examination. The other organs were normal.

The survival of such an animal for such a period of time strongly confirms the findings of Banting and Best. It also indicates, as far as is possible under the conditions of such an experiment, that the iletin of the Lilly Company represents the full endocrine potency of the pancreas and has not lost in the process of purification any substance that might be necessary for the life of a depancreatized dog.

2. Partial Pancreatectomy

Dog No. 49, a female mongrel in good condition at a weight of 12 kg., was subjected to a partial pancreatectomy in which the tissue removed weighed 15 gm. and the remnant about the main duct was estimated at 1 gm. Heavy glycosuria ensued on mixed diet, and after two weeks a ration was standardized in the form of 200 gm. lean meat and 50 gm. dry crackers daily. During a week the urinary sugar ranged from 16.8 to 28.9 gm. daily, and the plasma sugar from 0.390 to 0.500 per cent at various times in the 24 hours. A preliminary test was made of the influence of insulin upon this condition. Without food, the experiment was performed as shown in table II.

TABLE II.

Dog No. 49.

Insulin Injections in Partially Depancreatized Dog.

Time	PLASMA mg. per 100 cc.			URINE		Insulin injected subcutaneously
	Sugar	NaCl.	Urea	Sugar	Acetone	
8:45 A. M.	455	616	72	Heavy	neg.	
9:05						2 units
10:05	238					
11:32						1 unit
12:30 P. M.	86	585	54			
6:00	95	606	45			
11:30	129		36			
11:00 A. M.	168			5 gm. in 24 hr.	neg.	

The dog was strong and lively, and the insulin injections made no perceptible clinical change. The marked reduction of plasma sugar is evident, but no exact comparisons can be made with the totally depancreatized dog because of the difference in nutritive state.

The line of experimentation, to which this observation was meant to be preliminary, had to be postponed until the supply of insulin should become larger.

3. Diabetic Coma.

Dog No. 35, a black mongrel aged about 18 months, weighing 11.3 kg. in an excellent state of nutrition, was partially depancreatized on June 19, 1922. The tissue removed weighed 16.3 gm. The remnant about the main duct was estimated at 1.4 gm. (1/14). For certain reasons, it was proposed to produce acidosis in the animal, and for this purpose an abundant mixed diet of meat, bread and suet was given. Accordingly, by August 13 the dog had been fattened to a weight of 12.7 kg. and was strong and lively, though at the same time heavy glycosuria, moderate acetonuria, hyperglycemia and intense lipemia were present. At this point the plan originally made was abandoned in favor of a trial of the effect of insulin upon experimental coma.

A regular diet was therefore begun of 200 gm. of lean meat, 100 gm. of suet, 50 gm. of crackers, and enough talcum powder to control diarrhea. It was desired to give a larger quantity of fat, but this was impossible, as the dog had already acquired the usual distaste for it. Allen[2] has described the technique of such experiments, and also noted that the dog, which is less easily subject to acidosis than man, can be thrown into diabetic coma only if the digestion of sufficient quantities of fat is successfully kept up. It soon became necessary to feed the fat forcibly, allowing the animal to eat the rest of the diet subsequently. As acidosis increased and malaise and weakness began to appear, all food was refused, so that it became necessary to feed the entire diet forcibly and then sit with the dog for several hours continuously to prevent vomiting.

On account of frequent contaminations, few quantitative analyses of the urine were made. The reactions for sugar and acetone continued heavy. Also, toward the close marked albuminuria (3 8 per cent by Esbach) and numerous large granular casts made their appearance. The five analyses obtained for urinary acetone, and also the blood findings, are

TABLE III.

Dog No. 35.

Analyses in Pre-Coma Period.

DATE	URINE gm. Acetone	PLASMA mg. per 100 cc. Sugar	Acetone	NaCl.	Creatinin	Urea	Phosphates
Aug. 13		300					
" 14							4.7
" 17		300					
" 19		326	51				
" 20		375	59				
" 21		405	76			40	
" 22		405	59	552			4.3
" 23		332	62			16	
" 24		405	55	515		10	4.3
" 25	7.9	332	204				
" 26	7.2	416	104	490	1.7	14	
" 27		518	328	494	1.6	13	
" 28		600	258	476			5.0
" 29	4.5	526	83	461			
" 30	3.0	476	37	413			
A. M. 31	3.4	544	144				

TABLE IV.

Dog No. 35.

Insulin Treatment in Diabetic Coma.

Time	PLASMA ANALYSES						CORP. VOL.		REMARKS
	Sugar mg. per 100 cc.	Acetone mg. per 100 cc.	CO_2	Nitro-prusside Vol. %	NaCl mg. per 100 cc.	Creat. mg. per 100 cc.	Red %	White %	
8:30 P. M.	516	57	37.6	mod.			22	1	1 unit insulin at 9.20
10:20	600	70	37.6	mod.			23	1	2 units insulin at 10.30
11:35	450	56	36.2	mod.			21	0.5	3 units insulin at 12:00
Sept. 1									
12:45 A. M.	412	28	37.6	mod.			23	1	4 units insulin at 1:45 A. M.
2:45	326	98	31.9	mod. plus			23	1	4 units insulin at 4:00
5:30	199								
7:20	1000	45	22.3	neg.	423	1.7	21.5	0.5	5 gm. glucose and 8 gm. levulose intravenously
8:15	625		23.2	v. ft.					
8:30									10 gm. levulose intravenously. 20 gm. glucose subcutaneously
9:30									20 gm. levulose subcutaneously. 2 units insulin.
							Urea		
10:00	790	10	14.5	neg.	389	2.0	50		Dog died. Postmortem blood from inferior cava.

shown in Table III. The urinary ammonia, obtained by collecting perfectly fresh urine samples during August 29, amounted to 1.25 gm.

Toward the close the dog had a thin, feeble, anemic appearance, and the rapid fall in weight which occurred during the last few days was probably due in part to water loss. Nutrition had been kept up, however, to such an extent that the final weight under these circumstances was 11 kg. Increased depth of respiration became increasingly noticeable during the last week in August. Weakness and apathy were the outstanding clinical features. As noted by Allen, loss of consciousness occurs in the canine coma either later or in less marked degree than in human cases.

At 8 P.M. on August 31 the dog was found stuporous, dyspneic, and barely able to stand for a few seconds when placed on his feet. The eyeballs were soft, as in human coma. Incision to expose a jugular vein elicited not the slightest sign of feeling, and the circulatory failure was such that blood samples were difficult to obtain owing to the very poor filling of this vein.

In an unsuccessful attempt to save life, 16 units of insulin were given over a period of thirteen hours, from 9 P. M. on August 31 to death at 10 A.M. on September 1. Except for about 20 cc. voided at 11 P.M. and lost, no urine was secreted during this time. The blood analyses for the period are shown in Table IV.

From 6.30 A. M. onward, the dog was completely unconscious and limp. Convulsive gasping at 7.20 A. M. seemed to herald immediate death, but intravenous injections of first 5 gm. glucose and then 8 gm. levulose in 10 per cent solution produced apparent benefit, perhaps only through the increase of circulating fluid.

At 8.30 A. M., 10 gm. levulose was injected intravenously and 20 gm. glucose subcutaneously. At 9.30 A.M. 20 gm. levulose was injected subcutaneously, and 2 units of insulin at the same time in a different part of the body.

Death occurred by respiratory failure at 10 A.M., and the body was opened and blood and tissue samples taken while the heart was still beating. Specimens of liver, heart and skeletal muscle were taken for chemical and microscopic examinations for glycogen. The pancreas remnant, normal in

appearance and consistency, weighed 3.9 gm., indicating considerable hypertrophy since the estimate of 1.4 gm. on June 19. The liver was extremely large and fatty. All other viscera appeared normal.

The following features may be noticed in tables III and IV.

Plasma sugar. — In general the plasma sugar, determined in the mornings before feeding, tended to rise in the period up to August 31. The most striking feature of the observations shown in Table IV is the very marked resistance of the blood sugar to the influence of insulin. The initial level of the blood sugar was comparable to that in dogs 89 and 49, previously described. A reduction was accomplished, but only by means of far higher insulin dosage than would have sufficed to throw a totally depancreatized dog into hypoglycemic collapse. The values in this coma animal never went below the hyperglycemic level of 0.199 per cent. This marked reduction is, however, to be attributed strictly to the insulin injections, since the blood sugar of partially depancreatized dogs with severe diabetes and especially with acidosis does not fall spontaneously before death.

Acetone. — Instead of increasing, the acetone elimination diminished during the days when coma was approaching, and this diminished output did not run parallel to any retention as judged by the plasma acetone analyses. During the period shown in Table IV, with anuria, the plasma acetone values fluctuated independently of either the plasma sugar or the plasma bicarbonate, and in the postmortem blood the nitroprusside reaction was negative and the analysis for total acetone yielded only 10 mg. per 100 cc. These changes in acetone are not necessarily connected in any way with the insulin injections, as Allen has found that reduction and even complete disappearance of acetone are common occurrences in dogs dying of diabetic coma.

Plasma bicarbonate. — The CO_2 combining power of the plasma started at a level of 37.6 volumes per cent at 8.30 P.M. on August 31. This figure is not necessarily fatal, as far as can be judged from the information concerning acidosis, acapnia, etc., in the literature. The CO_2 values also showed complete independence of the plasma sugars and the insulin injections, and practically an opposite relationship with the acetone an-

alyses to what might have been expected theoretically. The decline of the bicarbonate as death approached is characteristic, and its independence of any accumulation of acetone bodies seems to be worth emphasizing.

Plasma chlorides. — In the pre-coma period shown in Table III, the plasma chloride concentration fell gradually as the clinical condition became worse. This fall continued to death, as shown in Table IV. This is the same behavior observed in some other fatal conditions in this Institute, and it will be commented on more fully in later publications.

Blood urea, creatinin, and phosphates. — These seemed to show no significant changes. The period of anuria resulted in only a trivial increase to 2 mg. creatinin and 50 mg. urea.

Corpuscle volume. — This was low, apparently indicating anemia. As it did not change appreciably, the changes in the various chemical analyses can scarcely be attributed to alterations of blood volume.

Insulin treatment. — The injection of 1 unit at 9.20 P.M. failed to prevent the rise of the plasma sugar to 0.600 per cent at 10.20 P.M. Four subsequent injections raised the total dosage by 2.45 A.M. to 14 units, and the plasma sugar at 5.30 A.M. was thus reduced to 0.199 per cent. The sugar injections already mentioned were given in the hope of aiding the animal to stand the large insulin dosage without injury, and if possible to supply food for strength and carbohydrate for combating acidosis. The animal was slightly benefited by the fluid thus administered, notwithstanding the great rise of blood sugar, but no other effect seemed perceptible. No clinical benefit was evident from the insulin injections mentioned, nor from an additional 2 units given at 9.30 A.M.

Glycogen of organs. — Weighed portions of liver, heart and thigh muscles were immediately cut up with scissors into boiling water. No opalescence and no reaction to iodine appeared. Potassium hydroxide was then added to a strength of 30 per cent, and the tissues hydrolyzed by boiling. The usual methods then applied to different samples yielded no glycogen reactions and no reducing sugar after heating with hydrochloric acid. Some mistake probably occurred, however, for microscopic specimens fixed in alcohol and stained with Best's carmine

through the kindness of Professor F. B. Mallory of Boston showed a distinct slight sprinkling of red granules in the heart and skeletal muscle and in the periphery of the hepatic lobules, the larger area in the center of the lobules being glycogen—free and moderately fatty. Glycogen was therefore present only in small traces, but probably sufficient to respond to delicate chemical tests.

Insulin, therefore, failed to save a dog in the late stages of diabetic acidosis, death occurring notwithstanding a very great reduction of both sugar and acetone and an absence of any demonstrable chemical cause for the fatal outcome. The same conditions may be expected to hold for the most extreme forms of human diabetic coma. Presumably, unknown secondary changes have occurred in these extreme states which render the clearing up of the primary diabetic disorder useless.

Conclusions.

1. The report of Banting and Best concerning the effect of pancreatic extract upon totally depancreatized dogs is confirmed, inasmuch as a dog which was in very poor condition at the outset was thus enabled to survive total pancreatectomy for one month, the operative wound healed rapidly without suppuration, and glycosuria, weakness, and other diabetic symptoms were strikingly abolished by the injections. This experiment further shows that the iletin prepared by the Lilly Company contains the pancreatic hormone necessary to support the life of a depancreatized dog, up to the time when death occurs from digestive deficiency due to the lack of the external pancreatic secretion.

2. The observations of Macleod and collaborators are also confirmed as regards the occurrence and symptoms of hypoglycemic collapse following overdosage of insulin, and the susceptibility of depancreatized dogs to this condition. These symptoms in diabetic dogs are relieved by sugar injections, in the manner described in rabbits.

3. The insulin requirement of a totally depancreatized dog weighing between 8.5 and 9 kg. in an emaciated state was found to be approximately 6 units per day. Owing to the uncertainties of digestion, this dosage cannot be brought into

any definite relation with the diet. The giving of the entire quantity within a few hours produced stormy results of collapse followed by return of glycosuria, even when the day's food was given at about the same time, while spacing the administration in the form of 1 unit every four hours gave a fairly uniform control of both glycosuria and hyperglycemia. This result may be instructive for the more severe forms of human diabetes, or it may be partly due to the poor digestion of the depancreatized dog.

4. Heavy glycosuria and hyperglycemia were abolished in a partially depancreatized dog by 5 units of insulin, but the observations on such animals were left incomplete.

5. A partially depancreatized dog dying of diabetic coma was not saved by the injection of 16 units of insulin, though the blood sugar was reduced nearly to normal, the acetone nearly disappeared, and no chemical reason for death was apparent. The plasma bicarbonate fell progressively to death and was entirely independent of the acetone values, the insulin injections, and the blood sugar changes. Traces of glycogen were found almost equally in the liver, heart and skeletal muscle at autopsy. It is assumed that the insulin treatment fails in advanced coma because unknown secondary changes prove fatal in spite of the clearing up of the primary diabetic disorder.

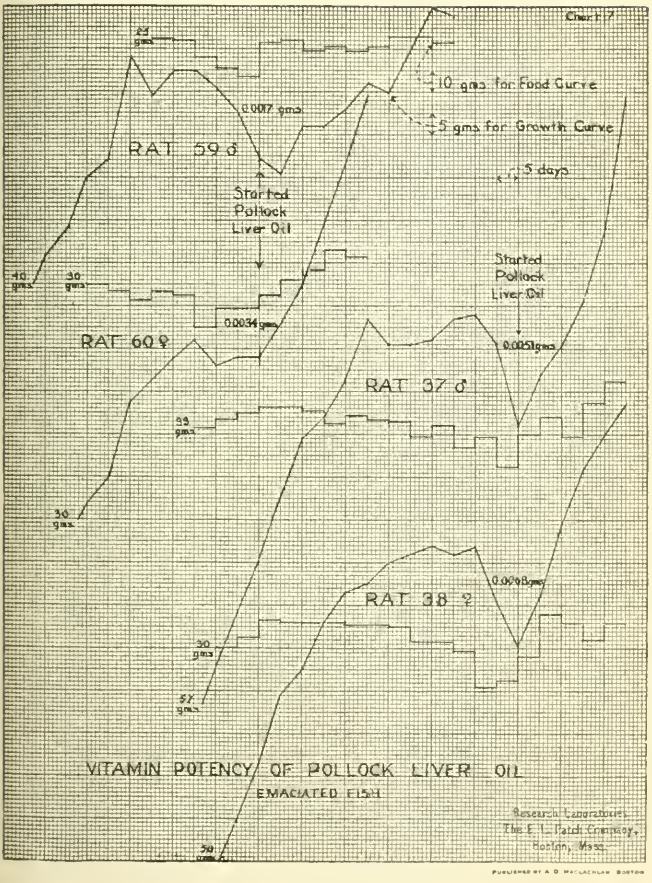
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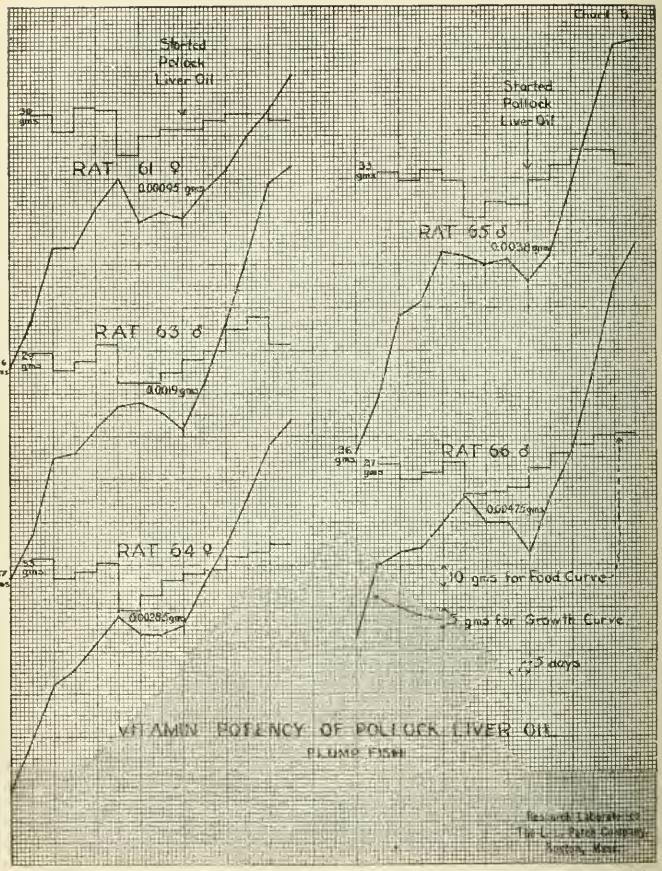
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The following notice is published at the request of the Department of Biology, Georgetown University, Washington, D. C.

THE DOCTOR SOFIE A. NORDHOFF-JUNG CANCER RESEARCH PRIZE.

Dr. Sofie A. Nordhoff-Jung of Washington, District of Columbia, United States of America, has founded an annual prize of five hundred dollars bearing the title of "The Sofie A. Nordhoff-Jung Cancer Research Prize". This prize is destined for the encouragement of researches in the etiology, prevention and treatment of cancer. It will be awarded by a commission, composed of members of the University of Munich, Bavaria, and be granted for the first time in December of the year nineteen hundred and twenty-three. The commission consists of Professors Borst, Doederlein and Sauerbruch with Professor von Romberg as chairman. This body is empowered to elect successors. The award will be made as a recognition of the most conspicuous work in the world literature bearing on cancer research, done at a time antecedent to the allotment of the award. Though the prize will not be awarded on a competitive basis the commission invites all research workers in cancer to submit literature on this subject.


Chart 7
10 gms for Food Curve
5 gms for Growth Curve
5 days
RAT 59 ♂
0.0017 gms
Started Pollock Liver Oil
RAT 60 ♀
0.0034 gms
RAT 37 ♂
Started Pollock Liver Oil
0.0051gms
RAT 38 ♀
0.0098gms
VITAMIN POTENCY OF POLLOCK LIVER OIL
EMACIATED FISH
Research Laboratories
The E. L. Patch Company,
Boston, Mass.
PUBLISHED BY A. D. MACLACHLAN BOSTON


Chart 6
Started Pollock Liver Oil
RAT 61 ♀
0.00095 gms
RAT 63 ♂
0.0019 gms
RAT 64 ♀
0.00285 gms
Started Pollock Liver Oil
RAT 65 ♂
0.0038 gms
RAT 66 ♂
0.00475 gms
10 gms for Food Curve
5 gms for Growth Curve
75 days
VITAMIN POTENCY OF POLLOCK LIVER OIL
PLUMP FISH
Published by A. D. MacLachlan, Boston

FEEDING EXPERIMENTS ON RATS WITH PLANTS AT DIFFERENT STAGES OF DEVELOPMENT.

I. Experiments with corn.

By BENJAMIN HARROW and FRANCES KRASNOW

Biochemical Laboratory of Columbia University, at the College of Physicians and Surgeons, New York.

The general consensus of opinion is that vitamines are synthesized in the plant kindom. Bottomley began a series of experiments in 1914 to show that the growth of green plant is accelerated by minute quantities of some organic substance to which the name "auximone" was given. This "auximone" (or vitamine?) is synthesized during the bacterial decomposition of peat.[1] Fürst[2], and later Chick and Delf[3], made the very important practical observation that when dried peas and lentils are germinated, their vitamine *C content* is much increased. Lately a number of American investigators, among them Williams[4], Funk and Dubin[5], McCollum[6], and Nelson and Fulmer[7], have busied themselves with the problem of the vitamine requirements of yeast. Some claim that yeast is able to synthesize vitamine *B*, whereas others deny the claim.

Drummond[8] has attacked the problem in a somewhat different way. He has determined the vitamine *A* content of a number of plant tissues at different stages of their development, and claims that whereas etiolated seedlings contain negligible quantities of this vitamine, the green seedlings contain appreciable quantities; from which he concludes that "the formation of the large amounts of vitamine *A* found in the green leaf of most plants demands the influence of light. Wilson[9], one of the latest investigators in this field, takes issue with Drummond, for he states that "either etiolated or green wheat sprouts furnish an adequate amount of vitamine *A* when the dried sprouts make up five per cent of the whole diet of rats. Inasmuch as this proportion of sprouts represents a quantity of seeds which, if included in the diet, would be in-

adequate as a source of this vitamine, the conclusion is drawn that vitamine *A* is produced in the growing plant with or without any photosynthesis".

Our own work, suggested by Prof. W. J. Gies, was begun some two years ago. Our object was the very broad one of tracing any increase in the vitamine content of the plant, beginning with the seed and ending up with the flowered product. The work is still in its preliminary stages, but it has been thought advisable to report what has so far been accomplished.

Our original intention was to use the lupin as the first of the seeds to be tested. We soon found that animals refused to eat the germinated seed. We then discovered that the germinated material was extremely bitter to the taste. This led us to substitute white corn (Stowell's Evergreen, procured from J. M. Thorburn & Co., N. Y. City), and the experiments that are recorded here have all been done with this corn.

Comparison of germinated and ungerminated corn.

Three groups of rats, four to a cage, were used. They were all from the same litter. The diets were as follows:

Group I.	Group II.	Group III.
Synthetic diet Vitamine A (codliver oil five per cent) Vitamine B (marmite two per cent)	Synthetic diet Germinated corn (five per cent)	Synthetic diet Ungerminated corn (five per cent)

The synthetic or "basal" diet consisted of casein (Harris' purified product, which was further heated at about 105°C. for 24 hours), 18 per cent; corn starch (Duryea's), 54; lard (heated and oxidized for 24 hours), 24; salt mixture, 4; water, 300 cc. Fresh portions of synthetic diet were made up every other day, and when not in use, the food was kept in the ice chest.

The corn was kept in water overnight and then divided into two parts: part I was air-dried and ground; this constituted the ungerminated corn; part II was germinated on sphagnum moss which had been previously boiled in water for six to

eight hours, and then washed in running water. The corn was covered with muslin (which had first been boiled) and then with a thin layer of moist sphagnum. This was kept for about three days when the weather was fairly mild. In our later experiments the germination was carried on in an incubator (kept at 37°C.) for about 20 hours. The seeds were then air-dried and ground. These constituted the germinated corn. The results of the experiments are given in Chart I.*

In the course of 52 days the percentage increase in weight of the rats was: group I, 91.7; group II, 51.5; group III, 52.5. It would seem, therefore, as if no compound (or compounds) obviously essential to the growth of rats is produced during germination — a result which confirms what we found a year earlier.

Somewhat later this problem of the effect of germination was attacked from a different angle. Here Funk and Dubin's method of determining the vitamine *B* content of products by their effect on the rate of growth of yeast[10] was adopted. For details of the method we must refer the reader to the original paper.

25 gm. of the dried corn, whether germinated or not, was mixed with 125 cc. of distilled water, shaken in the shaking machine for nine hours, kept in the ice-box overnight, and autoclaved at ten pounds pressure for ten minutes. The ungerminated product before autoclaving was a white, opalescent solution, which could not be obtained clear even on centrifugation; whereas the germinated product was a clear, yellow solution. After autoclaving, precipitates appeared in both of the products. The test solutions consisted of the supernatent fluids. The results may be tabulated as follows:

* The number at the beginning of each of the curves denotes the average weight of the rats when the experiment was begun. For the sake of brevity, a preliminary period in which rats were fed on a normal diet is not shown in any of the curves; but in no instance was a rat employed that did not grow normally on a normal diet.

(A and B represent duplicate determinations)

	1	2	3
	Yeast + Naegeli + water (control)	Ungerminated + Naegeli + water (control)	Ungerminated + Naegeli + yeast
A	1 c. mm.	0.0 c.mm.	17.5 c.mm.
B	1.2 c.mm.	0.0 c.mm.	17.0 c.mm.
		Germinated + Naegeli + water (control)	Germinated + Naegeli + yeast
A	—	0.0 c.mm.	18.0 c.mm.
B	—	0.0 c.mm.	18.0 c.mm.

This again leads to the conclusion that the growth factor in corn (vitamine *B*, vitamine *D?*) is probably not increased on germination. Since rats do not seem to need vitamine *C*, we cannot discuss the growth of this vitamine in the course of germination.

Comparison of alcoholic extracts of germinated and ungerminated corn.

It was considered not unlikely that an 80 per cent alcohol extract of corn, — which theoretically should extract not only vitamine *B* but also any vitamine *A* which the corn may contain — would yield better results than the whole corn, since much material other than the vitamine would remain in the residue. With this in view, the following experiments were carried out:

50 gm. of the dried, ground material (germinated or ungerminated corn) was mixed with 100 cc. of 80 per cent alcohol and allowed to stand overnight, being well shaken from time to time. This was then filtered and the filtrate allowed to drop on 50 gm. of corn starch. The product was dried in a vacuum oven and powdered.

It will be seen from an inspection of chart II that the addition of a five per cent alcoholic extract of germinated corn

to the basal diet does not prevent rapid decline, but that with an alcoholic extract of ungerminated corn there is at first a very appreciable increase in weight, followed ultimately by rapid decline. The substitution of the residue that remains after the alcoholic extraction for the alcoholic extract itself, causes substantial recovery. We must conclude, therefore, that under the conditions of the experiment, very little vitamine is extracted by 80 per cent alcohol, almost all of it remaining in the residue; and that this is particularly true of the germinated product. (See also chart VI, illustrating the addition to the diet of increasing quantities of alcoholic extracts of germinated corn.)

Subsequent experiments using more dilute alcohol (70, 60 and 50 per cent; see Chart III) indicate that even 50 per cent alcohol fails to extract appreciable quantities of vitamine.

We were next interested in determining what the deliberate additions of either vitamine *A* (five per cent codliver oil) or vitamine *B* (two per cent marmite) to the alcohol extracts would do. We thought it not unlikely that it might lead to information regarding the absence in the alcoholic extracts of some one definite factor.

The results are given in Chart III. They are such as to confirm the opinion that the alcoholic extracts contain little, if any, vitamine; for these results are analogous to what may be expected when either a synthetic diet and vitamine *A* or a synthetic diet and vitamine *B* are given to rats, without any further additions of alcohol extracts.

A comparison of ungerminated, germinated and seedling stages of corn in the undried conditions.

So far our experiments had been conducted with material that was dried before use. There was, of course, the possibility that fresh or "undried" material would behave differently. The varieties of corn were prepared as follows: The corn was soaked in water overnight, washed, and part of it dried superficially between blotting paper; this constituted the "ungerminated corn". The remainder was placed in a pot containing sphagnum that had been boiled and thoroughly washed, covered with filter paper and then with a thin layer of moist sphagnum, and kept in the incubator for about 20 hours. At

the end of this period a portion of the corn was removed; this was used as the "germinated corn". The filter paper was now removed from the remaining corn, which was next covered with a thin layer of moist sphagnum, and the pot placed in the sunny part of the room. In favorable weather, the early seedling stage, showing chlorophyll formation, was reached in three days, and the advanced seedling stage, with developed plumules, showing two to three leaves, in five to six days.*

The results are of a higly unexpected character (see Chart IV). Let us first examine the curve representing germinated corn. The initial growth was similar to the one obtained with dried germinated corn (see Chart I). There was a sudden loss of weight on the 28th day and one rat died five days later. As the remaining three rats continued to lose weight, the quantity of corn was increased to ten per cent on the 49th day of the experiment. This did not improve matters. Loss of weight continued. One of the rats showed sore eyes. The hind legs of another rat became badly paralyzed; it died shortly afterwards. An autopsy revealed nothing beyond an inflated intestine. The two remaining rats were put on the regular laboratory diet for rats. One of them was in such a poor state of health, that it died several days later.

Now let us turn to the rats fed on ungerminated corn (Chart IV). The curves representing the effects of germinated and ungerminated corn are strictly comparable, since they deal with rats obtained from the same litter, and the experiments were begun at the same time. Note the initial growth and the subsequent sharp decline in both curves. Note that in neither case does an increase in the proportion of the corn from five to ten per cent improve matters. Since the moisture in the undried material constitutes about 50 per cent of the product, ten per cent of the undried corn shoul have been approximately the equivalent of five per cent of the dried material.

The result with corn seedlings is similar (Chart IV).

A search of the literature failed to throw any light upon this peculiar behavior of fresh corn. Dr. Funk referred us to an early paper of his[11] on the value of oats as food, in which a somewhat similar observation is recorded, though very briefly and without comment. We are tempted to adopt the theory

* We wish to thank Dr. J. B. Paton for much helpful advice as to the method of growing seeds.

that some toxic factor is involved[12], but we suggest this with the utmost reserve. More work is necessary before a decided answer can be given. At this point we merely wish to observe that the fresh material, whether germinated or in the early or advanced seedling stage, is extremely and disagreeably sweet.

Comparison of varying amounts of corn

In our earlier experiments we adopted the arbitrary standard of adding corn to the basal diet to the extent of five per cent. After it had been shown that rats will grow for a considerable length of time on such a mixture (whether germinated or ungerminated, but always in the *dry* state), the question naturally arose, what is the minimum for growth? Chart V represents a probable answer to this question. With *dried* material our arbitrary selection of five per cent was a happy one, since this seems to be the minimum necessary for growth. This, however, does not hold for undried material, where even with five per cent there is obvious decline.

At this point we wish to refer to one of Drummond's latest papers on the increase in the vitamine *A* content of plants during growth[13]. First let us tabulate some of our own results.

	(days)	7	14	21	28
Undried germinated corn (one per cent) (Chart VII)	62 (average wt. of rats in gms.)	66	72	73	73
Undried green seedlings (one per cent) (Chart IV)	64	67	66	67	
Dried green seedlings (one per cent) (Chart V)	78	82	86	88	90

These results show a tendency in favor of the green seedlings. But caution is necessary, since an initial increase in weight may often be the prelude to decided loss of weight, as the experiments with undried germinated corn clearly de-

monstrate (see Chart VII). When, therefore, Drummond gives us the following results:

	(days)	7	14	21	28
Etiolated maize (0.7 g.)	61 (wt. in gms.)	90	96	96	
Green maize (white) (1 g.)	61	65	70	75	83

we wish that he had extended his experiments to a much longer period. Were we to adopt Drummond's method we might conclude, at the end of the first month of experimental work, that rats gain on undried germinated corn and on the dried green seedlings; and that the rate of growth is about the same in both. This would be a very true picture of the condition of the rats during the first month, but not necessarily beyond that time; and we have already seen that it is not true of rats fed on undried germinated corn.

We wish to thank Professor Dr. W. J. Gies for his kind help and friendly criticism.

Summary

1. Under the conditions of the experiments, no evidence has been obtained to show that either vitamine *A* or *B* (or *D*?) is formed during germination.

2. The addition of dried corn (germinated or ungerminated) to a vitamine-free basal diet to the extent of five per cent, induces growth in rats for a considerable length of time.

3. Cold, alcoholic extracts of dried corn (using percentages of alcohol varying from 50 to 80) contain little, if any, vitamine, though the response (in rats) with an extract of ungerminated corn is slightly more favorable than with the germinated variety.

4. When in the place of the dried corn, the undried variety is substituted, there may be initial growth, but this is followed by loss of weight, and, often, eye trouble, paralysis and ultimate death. This applies to the ungerminated, germinated and seedling stages of corn.

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CHART I.

Comparison of Germinated and Ungerminated Corn.

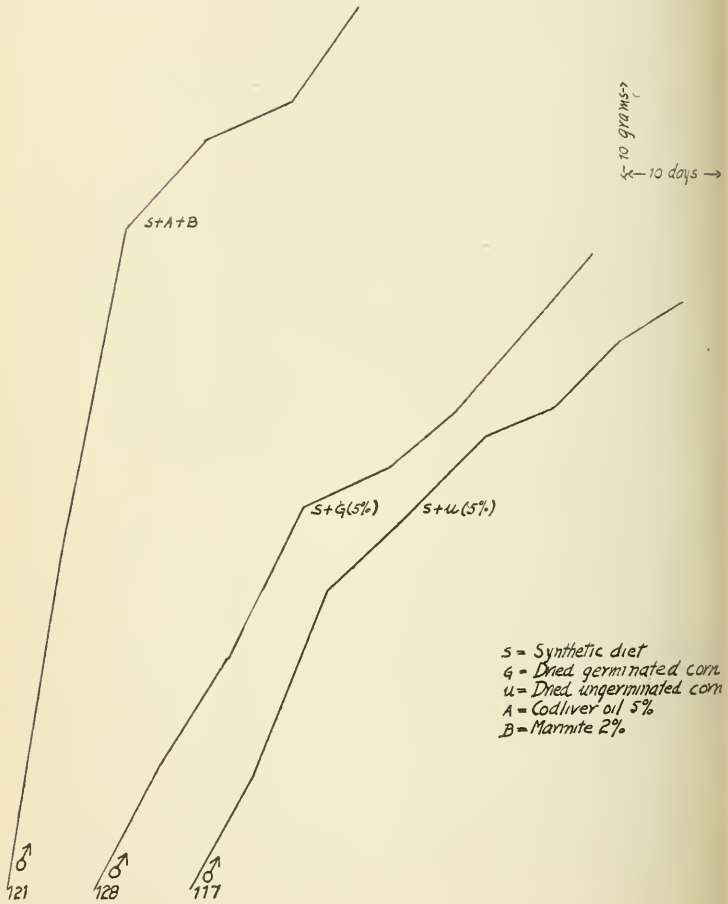


CHART II.

Comparison of Alcoholic Extracts of Germinated and Ungerminated Corn.

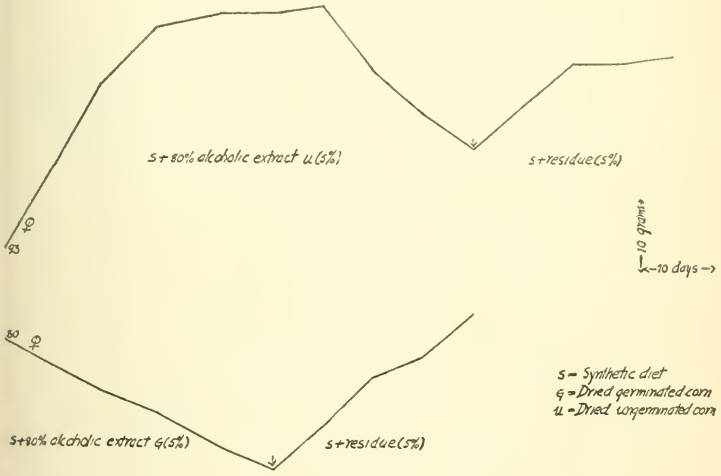


CHART III.

Alcoholic Extracts of Germinated and Ungerminated Corn.

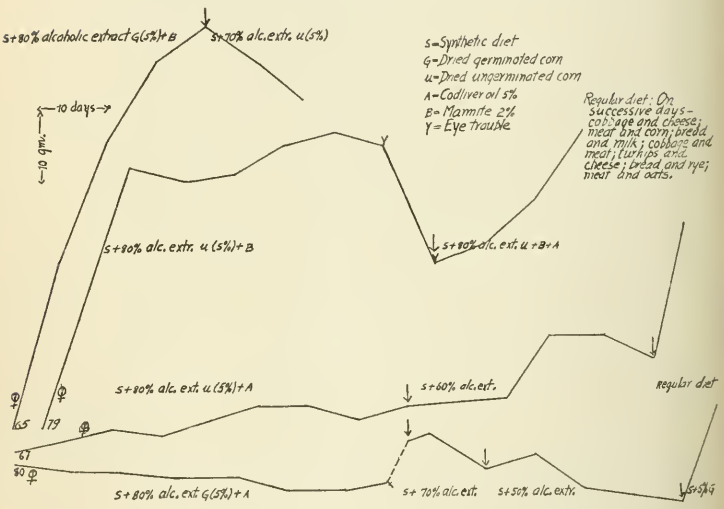


CHART IV.

Comparison of Ungerminated, Germinated and Seedling Stages of Corn in the Undried Condition.

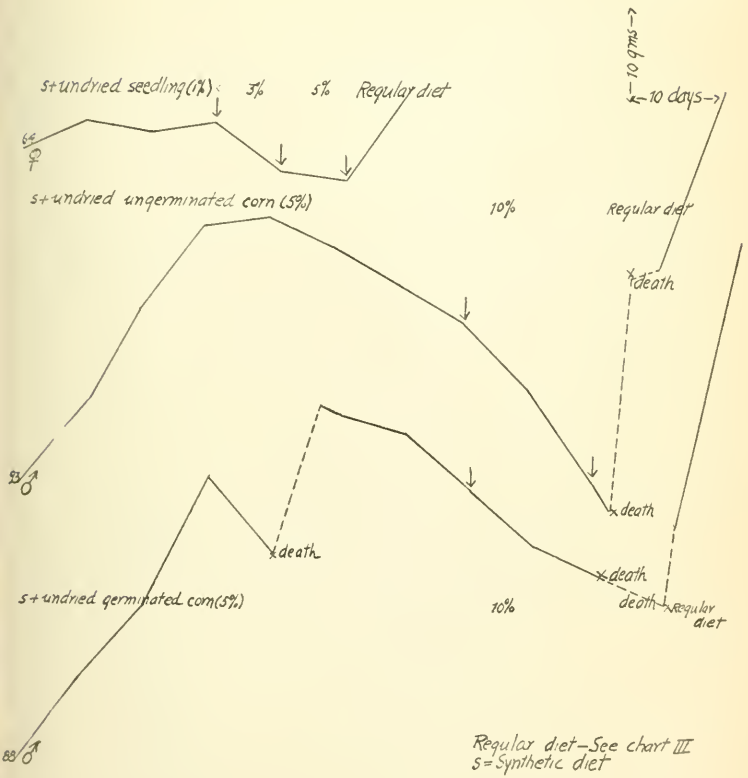


CHART V.

Comparison of Varying Amounts of Corn.

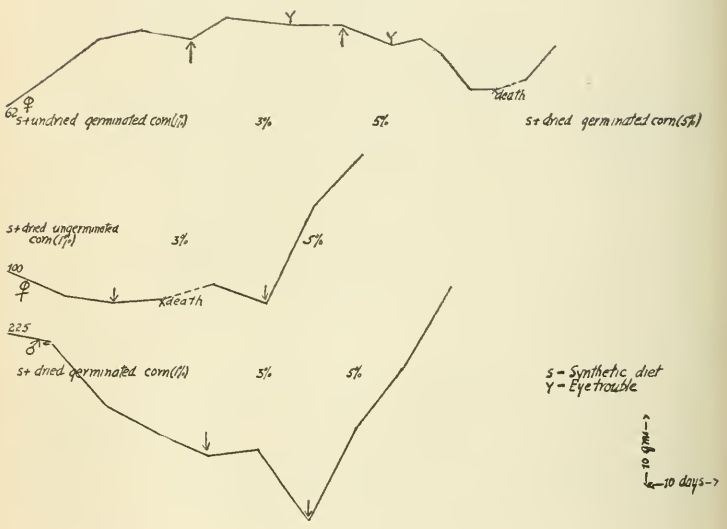
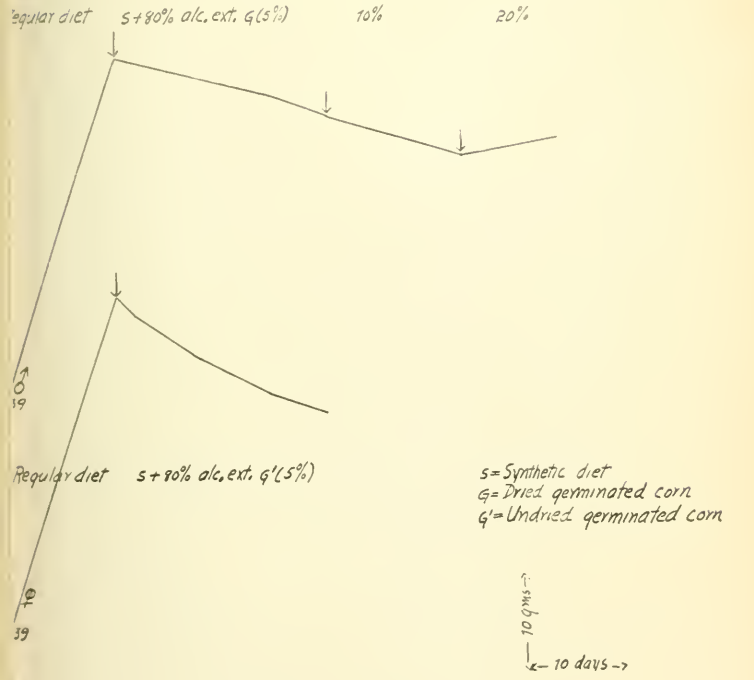


CHART VI.

Alcoholic Extracts of Dried and Undried Germinated Corn.



STUDIES OF THE THYROID APPARATUS

XI. The Effect of Thyro-parathyroidectomy on Reproduction in the Albino Rat.

By FREDERICK S. HAMMETT

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The existence of a physiological relation between thyroid activity and the internal secretory function of the female gonads is a matter of common observation. From this there has developed a vaguely defined hypothesis of a relation between thyroid function and reproduction.

Clarification is obtained if a distinction is made between the endocrine function of the interstitial gland of the female (stimulation of development of the secondary sexual characteristics; stimulation to sexual activity and possibly stimulation of the uterine mucosa in preparation for nidation) and the reproductive function (formation, maturation and discharge of the ovum) and ability to carry on to a successful termination the production of viable young. While it is true that there is apparently a close relationship between the endocrine function of the ovary and certain antecedent and terminal processes concerned in reproduction, there is evidence which tends to show that a normal intrauterine development of the fertilized ovum and delivery of viable young can occur when the ovaries have been removed from the pregnant female[1]. Moreover, there is no evidence that the presence of an endocrine product of either the male or female gonads is essential for fertilization.

Such being the case, it is necessary in an investigation of the effect of the loss of the thyroid function on reproduction to analyze the observations from the point of view of the reproductive processes subsequent to gonadal participation, as well as from the point of view of the gonadal endocrine phenomena associated with reproduction.

Before going on to the description of my studies in this field,

a brief review will be given of similar investigations from the point of view of comparative physiology.

Ceni[2] observed that the reproductive capacity of fowls was weakened by the loss of the thyroid function. Fewer eggs were laid, although those that were produced were somewhat larger than the normal. The chicks coming from these eggs showed developmental retardations and anomalies. Richon and Jeandelize[3] found that conception is possible in thyroidectomized rabbits. The young, however, die shortly after birth. The removal of the thyroid during pregnancy tended to lead to abortion, a confirmation of a similar finding by Lortat-Jacob.[4] Alquier and Theuveny[5] reported that the loss of the thyroid in dogs renders conception difficult and that the pups die soon after birth. Similar results were obtained by Frouin[6]. Palmer[7] found that partial thyroidectomy in pigs impaired the functions of reproduction although conception was possible. In a brief report Simpson[8] states that abortion and intrauterine death of the fetus occur in sheep after the loss of the thyroid. Evans and Long[9] were unable to detect any particular changes in the time of onset of sexual maturity or the oestrous cycle of albino rats after thyroidectomy. These observations are unfortunately invalidated by the fact that massive recurrences of the supposedly completely removed thyroid were found at autopsy.

Clinical reports suggest that thyroid deficiency in man is accompanied by disturbances in reproductive function. Wagner[10] cites the case of a woman 46 years of age who had not menstruated and in whom complete thyroid atrophy was present. Veil[11] reports several cases of myxedema in which, although conception occurred, the infants were either aborted, prematurely born or died at birth. Merguet[12] had a patient who was a cretin. She became pregnant and delivered the infant which died shortly after birth. Hergott[13] reports a case of myxedema in which birth was premature.

The general agreement in these observations on the different species shows that a deficient thyroid function in the female is accompanied by disturbances in reproductive ability. Two facts stand out clearly: the first, that conception is possible in the thyroidless female; and the second, that the products of conception of thyroidless females survive with difficulty if at all. The significance of this latter response will be discussed presently.

Previous investigators have largely confined themselves to the study of thyroidless females. The field of observation is consequently enlarged by my data on the results of mating completely thyroidectomized males and females; of mating partially thyroidectomized males with completely thyroid-

ectomized females, and of mating completely thyroidectomized males with partially thyroidectomized females.*

Although there is some evidence that the occurrence of a thyroid deficiency prior to the attainment of sexual maturity does not necessarily prevent the development of functioning gametes, it seemed worth while to include this phase of the problem in the present work. Consequently one series of rats used was thyro-parathyroidectomized when 56 days old and another at 45 days of age. These ages were chosen because histological studies of the gonads[14] have shown that the albino rat is sexually mature at two months or less, although Long and Evans[15] report that the average age at which the first ovulation appears is around 76 days. It may occur, however, much earlier.

The thyroidless animals were mated, one pair in each cage, and all received the same diet[16] and lived under the same environmental conditions. The rats were from the Experimental Colony "gentled" stock.[17] The male and female of each pair were kept together until a litter was cast or one of the pair had succumbed to the thyroid loss. If one of a pair died before conception occurred the survivor was mated with a similarly operated animal. If no litter was obtained up to the time the rats were 200 days old, both were killed and the examination for thyroid tissue made. The pups resulting from the successful matings were weaned when 25 days old and records were kept of their weights up to 150 days of age. All the mated rats were autopsied and record made of the presence or absence of thyroid and parathyroid tissue.

There was thus had two series of matings of rats deprived of their thyroid apparatus, presumably before sexual maturity had been reached. The results of theses matings are given in tables 1 and 2. In table 3 certain standard values are given for comparison.

* The partially thyroidectomized animals were those in which a small amount of thyroid growth was found at autopsy. This was never equal to more than a small fraction of the adult whole gland. Care was taken that no parathyroid tissue was left at operation.

TABLE I.

Data on the results of mating albino rats thyro-parathyroidectomized at 56 days of age.

Thyroid Residue		MATING NUMBERS																Total		%
Male	Female	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Yes	Yes	—	—	—	—	—	—	—	—	—	—	—	+	+	—	—	—	2		12.5
No	No	—	—	+	+	—	—	—	—	—	—	—	—	—	—	—	—	2		12.5
Yes	No	+	+	—	—	—	—	+	+	+	+	+	—	—	—	—	—	7		43.8
No	Yes	—	—	—	—	+	+	—	—	—	—	—	—	—	+	+	+	5		31.3
Age at litter		127	157	0	0	152	138	121	97	101	125	102	154	0	0	?	?			
Number in litter		8	6	0	0	12	7	11	8	6	2	8	5	0	0	10	11	89	Av. 8.1	
Lived until weaned		1	0	0	0	10	4	10	8	5	0	0	5	0	0	10	8	56	5.1	63.0
Died before weaning		7	4	0	0	0	3	1	0	0	0	8	0	0	0	0	3	26	2.4	29.2
Born dead		0	2	0	0	2	0	0	0	1	2	0	0	0	0	0	0	7	0.6	7.9
Av. birth weight		2.9	3.6	0	0	4.9	5.4	4.7	5.4	5.5	—	—	4.2	0	0	5 5	4.9			
Lived 150 days		1	0	0	0	0	4	10	8	5	—	—	5	0	0	9	8	45	4.1	50 6
Av. wt. 150 days																				
Males		140	0	0	0	0	257	104	211	258	—	—	246	0	0	272	209			
Females		0	0	0	0	0	182	168	202	215	—	—	193	0	0	155	176			

TABLE II.

Data on the results of mating albino rats thyroparathyroidectomized at 45 days of age.

Thyroid Residue		MATING NUMBERS									Total		%
Male	Female	1	2	3	4	5	6	7	8	9			
Yes	Yes	—	—	—	—	—	—	—	—	—	0		0
No	No	+	+	+		+	+	+	+	+	9		100.0
Yes	No	—	—	—	—	—	—	—	—	—	0		0
No	Yes	—	—	—	—	—	—	—	—	—	0		0
Age at litter		0	180	168	113	0	0	0	0	0			
Number in litter		0	3	7	1	0	0	0	0	0	11	Av. 3.7	
Lived until weaned		0	0	0	0	0	0	0	0	0	0	0	0
Died before weaning		0	2	6	1	0	0	0	0	0	9	3.0	81.8
Born dead		0	1	1	—	0	0	0	0	0	2	0.7	18.2
Av. birth weight		0	?	5.1	5.5	0	0	0	0	0			
Lived 150 days		0	0	0	0	0	0	0	0	0	0	0	0

TABLE III.

Comparison of observed results of breeding thyro-parathyroidectomized albino rats with standard values from unoperated normal animals.

	Observed values from rats operated at 56 days	Observed values from rats operated at 45 days	Reference Values	Source of Reference Values
Sterility	21.4	66.7	5.0* 28.8 20.8	Greenman and Duhring† King[18] Crampe[19]
Age at 1st litter	124	154	110* 111 - 121′ 116′	Greenman and Duhring† Donaldson[14] Long and Evans[16]
Number of young	8.1	3.7	9.4 7.0	Greenman and Duhring† King and Stotsenburg[20]
Average weight at birth	5.1	5.3	5.3 4.4	Greenman and Duhring† King[21]
Average weight at 25 days	Males 26.8 Females 26.4	—	Males 36.5 Females 34.4 23.9 25.4	Greenman and Duhring† Donaldson[14]
Average weight at 150 days	Males 207 Females 183	—	Males 287 Females 205 219 186	Greenman and Duhring† Donaldson[14]
Birth mortality	7.9%	18.2%	1.3 - 2.0%	King[22]

* Estimated values.
† Unpublished observations on the Experimental Colony stock.
′ Obtained by adding the average gestation period to age at which breeding begins.

An inspection of Tables 1 and 2 shows that the loss of the thyroid gland by either male or female or both, presumably prior to the attainment of sexual maturity, does not prohibit a development of the gametes to the point where reproduction is possible. Thyroidless males may impregnate thyroidless females; thyroidless females may conceive to partially thyroidectomized males, and thyroidless males may impregnate females in which a trace of thyroid tissue is present.

The reference values in Table 3, on which the comparison of the observed data is most logically based, are those furnished by Dr. M. J. Greenman from unpublished data, since the rats

used in my experiments came from the same group of animals and at the time my records were being made.

Table 3 demonstrates that the thyroidless females were more sterile and were older at the time of the first litter than their standards. The average number of young produced per litter was less and the birth mortality higher. Although the average weight at birth of both sexes combined was no different than that occurring in this stock, it is to be noted that the weight at 25 days of age (the time of weaning) was much less than that of the reference animals and that even a most favorable diet and environment up to 150 days failed to produce animals which weighed as much as did the rats from the same stock and under the same dietary regime, but of normal parents. This is suggestive of the possibility that the retardation of growth through undernutrition immediately after birth so affects the growth ability that complete recovery is unattainable. The data are too few, however, to be anything but suggestive.

It is evident that the loss of the thyroid apparatus reduced the viability of the young. This is shown not only by the relatively high birth mortality, but by the high death rate between birth and weaning, and the 19.6 per cent mortality which occurred between the ages of 25 and 150 days. (Table 1.)

All these differences were more marked in the animals thyro-parathyroidectomized at 45 days of age. In view of this fact and the observations of Miss F. Louise Duhring, Curator of the Colony, that the Experimental Colony rats breed at a much younger age than those of the Standard Stock, no conclusion can be made with regard to the possibility of the loss of thyroid function prohibiting the attainment of sexual maturity. It may well be that the removal of the thyroid apparatus from very young rats would result in an absolute cessation of gamete development and consequent inhibition of reproduction.

The results as a whole show that the loss of the thyroid function in young albino rats from 45 to 56 days of age does not prevent subsequent development of the secondary sexual characteristics, sexual activity or those changes in the uterine mucosa incident to nidation. Taken in conjunction with the observations from comparative physiology, they establish the conclusion that the internal secretory functions of the male

and female gonads are not disturbed to such an extent by the loss of or a deficiency in thyroid function as to inhibit their usual participation in the reproductive processes.

Turning now to the phases of reproduction concerned in the maturation of the gametes, there is an indication of a disturbance from the fact that the rats do not breed until they are quite a bit older than the usual breeding age for the stock from which they came. The smaller number of young produced may also be an indication of such a disturbance.

Going on to the effect of thyroid loss on the reproductive phase subsequent to fertilization it is plain that here, too, marked disturbance has been produced. There are fewer young, abortions occur, the birth mortality is high, and the weight of the young after subsistence on the maternal milk is much lower than that of the young of normal mothers from the same stock. These facts taken in conjunction with the data from other sources warrant the conclusion that the processes of reproduction concerned in the formation, maturation and discharge of the ovum are possibly, and the ability to carry on to a successful termination the production of viable young is decidedly interfered with by the loss of, or a deficiency in the thyroid function. It is evident that the processes of reproduction subsequent to gonadal participation are seriously disturbed by thyro-parathyroidectomy.

Are we justified in attributing these disturbances to the lack of a specific influence of the thyroid on the reproductive function? I think not: in the first place because, as shown in an earlier paper,[12] the removal of the thyroid apparatus from the albino rat tends to produce a condition of partial physiological inanition, which in turn is attributable to an inability to anabolize the food-stuffs presented due to the lack of thyroxin,[23] the specific stimulus to metabolism; in the second place because Long and Evans[24] found that the ovulatory performance of the rat is retarded by undernutrition, and Lusk[25] quotes Gaspard as stating that during the famine of 1817 in France the number of conceptions was reduced. Finally Troutmann[26] found that degenerative changes occur in the mammary glands after thyroidectomy which indicate a deterioration in lactating ability.

When these various observations are correlated, the conclusion is forced upon one that the disturbances in reproduc-

tion which obtain in thyroidless animals (increased sterility, greater age at first litter, high birth mortality, fewer young in litter and slower growth during nursing) are due, not to the lack of a specific influence of the thyroid function on the processes of reproduction, but to the general lowering of the metabolic level of the organism due to the lack of the thyroid secretion, which results in a condition of partial physiological inanition. In other words the results can be attributed to a nutritional defect.

I have purposefully omitted any consideration of a possible parathyroid effect in this study, since it has previously been shown[27] that the metabolic disturbances induced by thyroparathyroidectomy are different from those caused by parathyroidectomy alone and can be attributed almost if not entirely to the thyroid loss; and also because I am here dealing with chronic effects as distinguished from the acute.

Summary and Conclusions

Studies have been made of the reproductive ability of thyroidless albino rats.

It was found that conception occurred when completely thyroidectomized males were mated with completely thyroidectomized females; when partially thyroidectomized males were mated with completely thyroidectomized females, and when completely thyroidectomized males were mated with partially thyroidectomized females.

When the thyroid apparatus was removed from young rats 45 or 56 days of age, there was no apparent inhibition of function of the internal secretion of the gonads (stimulation to development of the secondary sexual characteristics, stimulation to sexual activity, preparation of the uterine mucosa for nidation).

The processes of reproduction concerned in the formation, maturation and discharge of the gametes were apparently disturbed by the loss or deficiency of the thyroid secretion, as were the reproductive processes subsequent to gonadal participation. This is shown by the increased sterility, greater age at breeding, high birth mortality, high mortality during and after weaning, the smaller number of rats in the litters,

and the failure of the rats to thrive during the nursing period as do the young of normal mothers.

From these results and from the point of view of comparative physiology it is concluded that the disturbances in reproductive ability following the loss of or a deficiency in the thyroid function are not due to any particular effect upon the endocrine functions of the gonads of either sex, or to the lack of a specific influence of the thyroid upon the processes of reproduction subsequent to fertilization, but that they are the result of the general lowering of the anabolic level of the organism due to the lack of the specific stimulus to metabolism supplied by the thyroid, which results in a condition of partial physiological inanition.

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THE TREATMENT OF ARTERIAL HYPERTENSION

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Introduction

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Classification of cases.
Summary of results according to decades of life.
Summary of results according to duration of treatment.

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Observations in 1918 and 1919, published as a preliminary communication[1] in 1920, furnished evidence in favor of sodium chloride restriction as a treatment for arterial hypertension. Records were there given of 20 cases thus treated, generally with marked benefit, also experiments showing the considerable elevations of pressure resulting from administration of salt and water respectively in certain cases. Attention was called to several details in this connection: (a) the high chloride concentrations (above 580 mg., often above 600 mg. per 100 cc.) in the plasma of the majority of untreated hypertension patients, and their good prognosis as compared with the smaller number of cases with low plasma chloride values (unless the latter values are disturbed by the coexistence of edema or diabetes); (b) the danger of supposing that accurate salt restriction is an easy matter, and the difficulty in the preparation of diets which shall be both appetizing and adequate; (c) the necessity of determining the sodium chloride ration required in individual cases, since the normal requirement does not necessarily hold good in pathological cases, yet too extreme restrictions will sometimes produce serious symptoms; (d) the limitations inherent in any treatment based on the principle of sparing a damaged function, so that a certain proportion of partial or complete failures must be anticipated, especially in cases with advanced organic changes.

In this publication reference was made to the advocacy of salt restriction for hypertension by Ambard[2, 3] and other French investigators[4, 5, 6, 7], and the general opposition or disbelief which their doctrine has encountered. This lack of acceptance seems to be explainable by the usual laxity in the practical application of both salt and fluid restriction, and by the obvious theoretical defects of the doctrine of "chloridemia," according to which the renal threshold for chloride and the resulting chloride retention should be the sole determining factors, and hypertension and its accompaniments, together with nephritic and puerperal "eclampsia," should yield regularly to salt privation. The poor success obtained in a few cases reported by others, particularly by German writers[8, 9, 10, 11], sufficed to discredit this therapeutic claim in most countries outside of France, and on the theoretical side the accumulating evidence of the importance of changes in

the general circulation, local or general alterations of permeability, etc., has overturned former ideas of the exclusive role of the kidneys.

Nevertheless, it should be noted that numerous cases of local or general hydrops fail to yield to salt privation, and the universal acceptance of salt-free diet as a practical treatment of edema and its nearly universal rejection for the treatment of hypertension seem to be due chiefly to the fact that success in the latter class of cases often requires a more strict and accurate exclusion of salt. Likewise, the theory of "chloridemia" has suffered less from later researches as applied to hypertension than as applied to edema; for chlorides are known to accumulate in edema fluids without any elevation of their concentration in the blood or of the renal threshold; also, though forms of hydrops without apparent renal lesions are numerous, it is improbable that hypertension ever occurs without abnormalities in the kidneys or their blood vessels.

An incomplete survey of the literature shows the following with respect to restriction of water and of salt respectively in hypertension cases.

Water Restriction

Von Noorden[12] was one of the earlier writers who turned against the use of milk diet for nephritis, particularly of the atrophic form. He described a case of this type in which stenocardia and dilatation of the heart developed on a milk diet which produced 3 to 4 liters of urine daily, and in which marked relief was obtained by a change to a mixed diet containing only 1¼ liters of fluid.

Volhard[13, 14] mentions dry diet as a long-tried routine measure for hypertension cases, particularly in critical emergencies. He also mentions the serious symptoms which may sometimes occur when water is given more rapidly than such patients can excrete it.

Miller and Williams[15] corroborated the observation that the drinking of large volumes of water raises the blood pressure of some hypertension cases. Mosenthal[29] objected that the quantities of water administered by Miller and Williams exceeded the usual physiological limits of intake, but this criticism lacks force in view of the clinical references above given, which could be multiplied if desired, and which Mosenthal has apparently overlooked.

Orr and Innes[16, 17] performed experiments by adding 2 or 3 liters of water on certain days to the regular diet of two healthy subjects, two others with slight hypertension and no other evidence of disease, and fourteen patients with pathologically high blood pressure. Proceeding from a definite assumption that protein decomposition products are responsible for elevations of blood pressure, they concluded as follows: "(1) Both in apparently normal subjects and in pathological cases with high arterial tension copious ingestion of water is followed

by a decrease in blood pressure. (2) It is suggested that the fall in pressure is due to the elimination of pressor substances that cause arterial constriction. (3) When diuresis is unable to keep pace with the intake of water, as may occur in renal insufficiency, the fall in pressure is preceded by a rise above the original level."

The reductions of systolic or diastolic pressure shown by these authors were generally not great; for example, before water 180/113, after water 172/112 and 156/101; before water 155/102, after water 151/101; before water 248/152, after 206/136, 231/153, 244/153. The best result, in a case of chronic Menière's disease, was 212/125 before water, 165/102 after. It was vaguely said that there is some tendency to a cumulative effect with continued water drinking. On the whole, the changes described are within the limits of the familiar fluctuations of blood pressure in such cases, and there is some theoretical interest in learning why water drinking should cause these fluctuations. A flushing out of salt would be a tempting hypothesis in the pathological cases, but would probably not explain the slight lowering of blood pressure in normal subjects. Some physical or mechanical process is probable, but there is no evidence for the supposition that this consists in a flushing out of nitrogenous products. The most important point is that no genuine or lasting benefit was demonstrated in any instance. Only a temporary symptomatic change is established, and it remains probable that excessive quantities of fluid will injuriously overtax the renal and circulatory functions, according to long-established clinical teaching. It is astonishing that such a method upon such inadequate support should be hastily taken up by various physicians and journals as a practical treatment for high blood pressure.

Salt Restriction

The treatment by salt-poor diet has continued in use in France, as may be found by reference to practically any French treatises.[18, 19] The textbooks of Oliver[20] and of Norris[21] are almost the only ones in English which make at least some doubtful recommendations of this method. The chief criticism against all these writers may consist in their deficient strictness and accuracy. Their silence concerning salt privation symptoms strengthens the belief that their diets were not exact enough for the best results in the severe type of cases, and to this reason the general skepticism regarding their views is probably attributable.

Nearly all the standard textbooks outside of France either fail to mention the salt privation treatment or specifically state that salt need not be restricted in hypertension cases without edema. This statement can be verified not only in the current compends of medicine, but also in the special texts or chapters of LeFevre,[22] Eichhorst,[23] Hasebroek,[24] Nicholson,[25] Hewlett,[26] Miller,[27] Munk,[28] Austin,[29] Mosenthal,[30] Warfield,[31] Siebeck,[32] Lichtwitz,[33] Eppinger and Kloss,[34] and Shaw.[35] Volhard[14] in a number of places mentions restrictions of salt as well as

water, especially for the treatment of acute emergencies in hypertension cases, but from illustrative cases[36] it is seen that the lax restrictions permitted a liter or more of water and 3 or 4 grams of sodium chloride daily even in such emergencies, and elsewhere[37] it is strongly emphasized that such restrictions are not advisable in simple or nephritic hypertension without edema. Medical journal articles on hypertension show complete neglect of any chloride factor, as may be illustrated by reference to Janeway,[38, 39] Miller,[40] Soper,[41] Mosenthal,[42] Moschcowitz,[43] Hirsch,[44] and others. MacCallum[45] likewise fails to mention salt in any relation to the subject of arteriosclerosis. In discussions of the subject of hypertension before the American Medical Association following the papers of Miller[39] in 1913 and of Foster[60] in 1922, not a single speaker advocated chloride restriction, as far as the published records show.

The observations or opinions elicited by our preliminary communication[1] may be divided into (a) favorable and (b) opposed.

Favorable Views

Musser,[46] defining essential hypertension as "a condition of continuous high blood pressure, systolic pressure over 175 mm. of mercury, of unexplained cause", published the following table of results of treatment with salt and water restriction:

	Blood Pressure, mm.	
	Before.	After.
Case I	185/85	125/75
" II	215/105	170/85
" III	157/79	130/80
" IV	204/115	170/105
" V	205/120	160/100
" VI	174/80	145/75
" VII	230/110	210/100

Konikow[47] described a marked fall of blood pressure during an attack of pneumonia in a woman with hypertension. The fall of chlorides in blood and urine during pneumonia is doubtless more rapid and marked than can be achieved in such a case by dietary restriction. In view of this association, however, the same patient was tried subsequently by Konikow and Smith[48] on salt-free diet. The case was a difficult one, but with the diet there was a gradual fall of the systolic pressure from 235 to 170, and of the diastolic pressure from 130 to 112 mm. There was also the usual relief of subjective symptoms, especially headache. Addition of salt to the diet raised the pressure to 225 systolic, 120 diastolic.

Higley and Field[49] have made laboratory observations, extending over periods of years, in numerous hypertension cases treated by vari-

ous physicians with salt-free diet. This group of physicians are convinced of the benefit of the method, which they use invariably in such cases, but as this paper deals with the laboratory side the clinical details are omitted.

Houghton[50] stated: "In an experience now large enough to warrant temporary conclusions, and especially in view of the publications of Allen and Musser, it has become increasingly evident that sodium chloride is the immediate and chief toxic agent, often associated, especially in those with high pressure, with excessive retention of water and possibly uric acid." His patients have generally presented a history of acute infectious diseases, sometimes with chronic sequelae. He considers that sodium chloride excretion is generally the first renal function damaged by such processes, and often the renal irritation is increased by gross excesses of salt in the diet. The frequent traces of albuminuria are one sign of such irritation. He also suggests that uric acid may be a factor in some cases of hypertension. He advises treatment by gradual reduction of salt intake, and mentions the privation symptoms sometimes observed when the allowance is made less than 2 gm. daily. "There is no department of medicine where attention to every detail is more necessary to achieve success." The mere order for a "salt-free diet" may suffice for edema but not for hypertension. "The pathological blood pressures of pregnancy may be treated likewise, provided the process is not too acute, although the limitations in this field have not been carefully worked out." High plasma chloride concentrations with normal blood pressures are found in such conditions as pulmonary tuberculosis and pernicious anemia, while normal plasma chloride values and high blood pressure are found chiefly in the "azotemic" type of nephritis. Records are given of ten hypertension cases treated with salt restriction, the pressures sometimes being reduced actually below normal. Difficulty was encountered in one case from such a seemingly small dietary error as the drinking of milk. The writer concludes that arterial hypertension is a tertiary condition, of which the immediate cause is a larger sodium chloride intake than the damaged kidneys can excrete. The responsible factor is supposed to be the sodium rather than the chlorine component. "If the hypertension does not become normal within a reasonable time, either the patient's diet is not below 2 gm. in sodium chloride content, which may be determined by a 24-hour urinary examination, or advanced anatomic nephritis is present which prevents rapid dechlorinization and dehydration. Time and proper diet will usually produce the desired results."

Stone[51] has stated: "My own experience in a very few cases has been encouraging as to the benefit which might be derived from a chlorine-poor diet," but has given no details of cases.

Opposed Views

McLester[52] reported as follows: "Following the suggestion of Allen that the chloride restriction of the past has not been sufficiently rigid,

study was made in a small number of hypertension cases of the effect of the almost absolute elimination from the diet of all chloride. The following results of such a diet were noted: 1. The patient found the food unappetizing and usually ate but little. 2. The blood urea, instead of decreasing, showed a tendency to increase. 3. The blood chloride, irrespective of diet, varied but little. 4. The systolic pressure as a rule showed a moderate fall; the fall was never marked. 5. In two of the patients there developed weakness and prostration to a distressing degree. 6. One of the patients suddenly experienced retinal changes and other fundus changes at the end of 2 weeks of this diet." The conclusion is reached that the almost complete elimination of chlorides from the diet of patients with chronic nephritis and vascular hypertension accomplishes nothing more than the salt-poor diet ordinarily prescribed.

This writer confessedly failed to make the salt-free diet appetizing or to keep patients on it for more than two weeks continuously, though both of these results are perfectly feasible with proper methods. He also ignored the warning[1] of the symptoms which may result from too extreme salt privation, and which call for an accurate small ration of salt instead of abandonment of the treatment. The other criticisms are associated with the brevity of the treatment and other minor details to be mentioned below. Retinal hemorrhage in conjuction with the salt-free diet is in our opinion accidental, as this diet ordinarily acts powerfully in checking retinitis. The greatest fault is to be found with the general conclusion, and with a related statement in another article of similar purport:[52] "I am led to believe that the excessive use of salt does real harm and that its restriction does good." As shown above, it is not a fact that any degree of chloride restriction is "ordinarily prescribed" for hypertension. The overwhelming majority of authoritative writers ignore or oppose chloride restriction altogether. It is unfortunate that McLester failed to publish any details of his unsuccessful cases, in order that they might be more closely examined, or of his successful cases, in order to furnish evidence that some degree of salt privation is beneficial. If the statements made are to be taken at their face value, they rank McLester among the upholders of salt restriction in the treatment of hypertension.

O'Hare[54] mentioned the evident fact that it is possible to furnish abundant calories with salt-poor diets. "Although our experiments are not yet complete they seem to be in accord with Dr. McLester's conclusion that a diet containing less than 0.5 gm. of sodium chloride does not reduce the blood pressure more than less radical measures. An interesting sidelight is thrown on the subject by a series of 45 or 46 cases of hypertension. These have been arranged according to the height of the maximum blood chlorides. These normal cases were largely cases of vascular hypertension, whereas those cases showing high blood chlorides were on the whole obvious nephritics with retention of nitrogen as well as salt. Curiously enough those cases that showed the normal chlorides averaged the higher blood pressure. Variation in pressure is the rule in hypertension and considerable drop

in pressure without the action of a given diet is not uncommon. One patient, and she is not a very unusual one, on a house diet with rest for 9 days showed a drop in pressure of 230 to 150 systolic and 140 to 80 diastolic. Any therapy offered for the reduction of blood pressure must be interpreted very conservatively." Previously, O'Hare[55] stated: "On general principles, it is well to restrict salt, condiments, alcohol and excessive tobacco."

Christian[56] gave a similar statement of opinion from the same clinic. "Another cause for hypertension, rather recently adduced, is that it results from a disturbed salt metabolism and can be satisfactorily treated by eliminating salt from the diet. Our studies at the Peter Bent Brigham Hospital have not supported this view. This is not to say that in some cases of hypertension we do not find poor salt elimination. This has long been recognized, but it is our belief, based on our own observations, that salt retention is dependent on a disturbed renal function and an accompaniment of some cases of hypertension rather than an important causative factor." Elsewhere, Christian[57] has recommended restriction of sodium chloride to 3 to 5 gm. daily as part of the routine treatment of both "pure" hypertension and of chronic nephritis without edema.

Judgment of the work of O'Hare and Christian is impossible before the publication of their detailed results, which should show the basis for their quantitative views of chloride limitation. O'Hare has evidently labored under a misapprehension in his comparisons of blood chlorides and blood pressures, for there is nowhere in the literature any claim of parallelism between the two. The errors involved in the early conception of "chloridemia" have already been mentioned, but the word is used in France to cover any chloride retention, whether in the blood or in the tissues.

Strouse[58] reported the case of a Russian Jewess aged 47 years, with systolic blood pressure of 290 mm. or more, and diastolic 160 mm. During the admission to hospital she had what appeared to be an attack of acute cholecystitis. In 10 days of bed rest on a diet low in protein and salt, the pressure fell to 260 systolic, 150 diastolic. The addition of 75 gm. protein and 10 gm. salt failed to halt the fall of blood pressure, which after ten more days had reached 200 systolic, 100 diastolic. On the ninth day an attack of intense abdominal pain failed to raise the blood pressure. Despite all further treatment she complained constantly of headache and general distress, and the blood pressure gradually went up in spite of milk or salt-free diet. The writer states that his general clinical results have failed to show any influence of either protein or salt upon blood pressure.

The single case described has little value as evidence, because of the powerful and irregular influence of infection, which is known sometimes to elevate blood pressure in spite of all dietary or other treatment, and again to lower it through weakness or prostration. The chief criticism of the general article is that it gives no data of the accuracy or the duration of the salt-free diets. The lack of any men-

tion of privation symptoms in any cases creates doubts of the actual strictness of salt exclusion.

Mosenthal[59] presents figures showing the absence of influence of protein upon blood pressure. He recognizes the reduction of hypertension by reduction of obesity in some cases, and is inclined to attribute the effects of salt-poor diet to undernutrition. He gives a table showing entire absence of parallelism between blood pressure and the sodium chloride percentage of whole blood in a series of normal and diseased conditions, the highest concentration, viz: 676 mg. per 100 cc. of blood, having been found in a patient with anemia and low blood pressure. Mosenthal and Short are quoted as having failed to influence arterial tension by administration of 10 gm. NaCl. Emphasis is placed upon irregularities of blood pressure due to rest, exercise, emotion, and other transitory causes.

The lack of parallelism between blood chlorides and blood pressures in sick or well persons without hypertension does not answer the question at issue, viz. the influence of chloride restriction upon cases with hypertension. It is self-evident that some organic or functional abnormality must constitute the basis of hypertension. It is also well known that the blood chlorides may be high in diseases without hypertension, and that much salt may be retained in edema cases without hypertension. It is obvious that persons lacking the particular organic basis of hypertension are not subject to hypertension from salt, and the actual question involved, viz: whether persons having this organic basis are subject to hypertension from salt, can be settled only by tests upon this particular type of individual. In a subsequent discussion before the Academy of Medicine in New York, Mosenthal mentioned his observations of symptoms from test doses of salt in certain cases, like those noted in our previously published salt tests[1], but he connected these theoretically with the nephritic element rather than with the hypertension element in these cases. There is no published record of any experience of Mosenthal upon which a therapeutic judgment can properly be based, viz. an exact report of an adequate series of hypertension cases treated by salt restriction over sufficient periods of time with suitable controls of the chlorides in blood and urine.*

* This statement is strengthened by the paper of Mosenthal and Short[61] which appeared during the correction of our page proof. As we suspected, the brief and imperfect exclusion of salt, revealed by their urinary chloride analyses, sufficiently explains their therapeutic failure, and is hard to understand in view of the plain warnings given by ourselves[1] and Houghton[50] on this point. Also our tests, proving that patients whose hypertension and symptoms have been relieved by chloride restriction, are subject to a return of high pressure and symptoms by the taking of 10 gm. or less of sodium chloride, differ fundamentally from the procedure of Mosenthal and Short, who gave such doses to patients who had had no relief under the inadequate treatment used. These negative results confirm our statements that the effects of small and large quantities of salt are often scarcely distinguishable, and only thorough and exact salt exclusion can give the benefits which so many physicians have missed by the use of inexact methods. The clinging to whole blood analyses for chlorides after they have been found worthless, and other details, have been sufficiently criticized. The radical disagreement between ourselves and other writers, whom we freely recognize to be in the majority, comes down unavoidably to a question of clinical accuracy, and on that basis we are prepared to await the

Foster[60] has laid stress upon the excessively active lives and surplus body weight of many hypertension patients, and upon treatment by rest, undernutrition, general regulation of diet with emphasis upon low protein, and hygienic regimes especially in sanatoriums. "The most definite characteristic of nephritis associated with hypertension is the tendency to store in the tissues nitrogenous bodies which should be excreted in the urine. For some time we have been utilizing this fact in the treatment of nephritis in general. The effect of low protein diets in some cases of chronic nephritis becomes apparent in the blood pressure curve, as well as in the general symptoms of the disease. Chart 4 is from a case of chronic nephritis, and shows the effect of restricting protein food to approximately 30 gm. a day. This change in diet was the only change in therapeusis made during this period. Previous to this period the patient had been kept at rest without any notable change in the blood pressure curve". "In regard to the salt-poor diet advocated from time to time, doubtless restrictions in salt are occasionally operative in reducing blood pressure. I doubt that it is the salt deprivation. From my observation, those who eat large amounts of salt are usually persons who eat an excessive amount of food, particularly of protein. If you restrict their salt, you destroy the appetizing feature of their food and they unconsciously eat less. It is because their food intake is less that one gets results from the salt restriction, and not because of the salt *per se*."

As hypertension is sometimes relieved by the correction of an accompanying diabetes, obesity or hyperthyroidism, so also it is conceivable that relief of an overtaxed nitrogen excretion may benefit other kidney functions and thus tend in some measure to reduce blood pressure. As renal irritation from high protein ingestion has been described,[61] and as Ambard himself[62] demonstrated mutual relations between the salt and urea functions, overstrain of one function impairing the other, it cannot be a safe doctrine that all hypertension patients may be dieted without any limitations of protein. This concession is the utmost required to cover exceptional observations of a protein influence, granting that they are correct. Foster doubtless knows that the entire literature contains not a single study of an adequate series of cases, showing elevation of pressure by protein excess and reduction by protein restriction. This unfounded tradition has been properly dismissed by such writers as O'Hare, Moschcowitz, Mosenthal, and Strouse[58a], and the masterly review by Volhard[14] suffices to exclude any known consistent relationship between blood pressure and nitrogen retention. It is always permissible for a dissenting individual to muster new evidence against a prevailing doctrine, but such evidence should consist of something more than one case. Foster's article admits occasional good results from salt restriction, but gives no accurate data of cases in which such restriction has succeeded or failed, and no proof of the supposition that the benefits in question are due to undernutrition.

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decisión. As a study of the rate of diffusion of new ideas or methods of treatment among the general medical profession, it will be interesting to observe how long it may take the Journal of the American Medical Association to retract the false conclusion of a recent editorial.[82]

The sole fact brought out in the published discussion of this paper was the observation of Palmer, that all of his patients, "regardless of the treatment they had received, whose diastolic blood pressure was over 120, were either in very poor condition or dead at the end of about two years", and the corroboration by Foster, "I agree with Dr. Palmer that the majority of cases in which there is an elevated diastolic pressure of 120 mm. of mercury are terminated at the end of two years." Mortality comparisons under different methods of treatment should be instructive.

The frequent recommendations of dry diets for cases with circulatory disorders, or especially for the critical emergencies in the course of such cases, betray loose dietary conceptions when no mention of salt restriction is made, for obviously the latter measure is necessary for the comfortable or safe application of the former. In this sense all the textbook writers who advise fluid limitation for hypertension might be included among the supporters of salt limitation. Our own work was first suggested by the cases with hyposthenuria and polyuria, the plan being to stop the excessive day-and-night strain upon the kidneys and circulation by omitting salt, thus obviating thirst and polyuria, and to observe the possible benefit to the blood pressure and other symptoms. The benefits obtained in such cases were then duplicated in cases without polyuria, and after the results were plainly established, reading outside the scope of current texts acquainted us with the pioneer French work in this field.

These clinical results furnish our main reason for considering hypertension as a unit.

The literature heretofore has mostly been dominated by opinions of the kind expressed by Christian[56]: "Hypertension very likely is, in a sense, of the nature of a symptom and not a disease, an expression of a disturbance that, like fever, may have many causes." The pathological doctrine, for which Volhard and Fahr deserve chief credit and which is accepted also by Christian, is that hypertension results from organic and functional injuries of the small blood vessels of the kidneys. General vascular lesions creating increased peripheral resistance to the circulation are a probable influential factor, and different degrees of injury in the different circulatory tracts may account for special disturbances in the various organs, but the primary and determining lesions are probably those in the kidneys, setting in action some mechanism for maintaining an efficient circulation against the increased local resistance. The outstanding chemical feature of such injury seems to be the altered permeability to substances with osmotic properties, of which sodium chloride is chief. The chloride re-

tention and the different vascular lesions interact to form a vicious circle; and the heart, which at first provides for circulation and elimination through increased labor, gradually fails under the increasingly heavy burden and the specific impairment of its own nutrition. This view of the pathology, which will be further discussed hereafter, recognizes infection or intoxication as the cause of the primary injury and of some exacerbations, as held for example by Emerson,[63] but emphasizes furthermore the progressive functional and organic damage arising secondarily from the vicious circle above mentioned (the hypertension or the cause back of the hypertension—Moschcowitz[64, 65, 66]). Diabetes has been regarded as a mere symptom by many writers, who were confused by the accidental variations and complications, until recently the unitarian doctrine of this disease has become safely established. A similar unitarian doctrine will regard hypertension as a clinical and pathological entity, without confusion on account of accidental associated or modifying conditions such as obesity, gout, diabetes, hyperthyroidism, pregnancy, cardiac disease, selerosis of the larger blood vessels, or disorders of the epithelial structures of the kidneys. The partial pathological evidence for such a unitarian doctrine is strengthened by the clinical observations of uniform response of all types of cases to a single method of treatment, the individual differences being sufficiently explained by the variable interplay of organic and functional factors.

The series to be presented comprises 180 cases, under observation for periods of four years at the longest and one month at the shortest. The selection has been limited to patients who had shown systolic blood pressures consistently above 175 mm. of mercury for some time prior to admission. Though the list could have been enlarged to well over two hundred by adopting a standard which would include lower or transitory elevations of pressure, and though we believe that these mild or incipient conditions present a highly important opportunity for therapy and prophylaxis, the more severe cases afford a more stringent test of treatment, and are relatively free from any long-continued changes due to small accidental factors. It is possible that some public or charity hospitals have a more unfavorable clinical material, because of the later stage at which the poor and ignorant seek medical care, and their inferior fidelity to dietary prescriptions. Nevertheless, the metabolic cases referred by physicians to a specialized institution are generally severe, often desperate in prognosis, and this series furthermore comprises a fair representation of all social grades, including charity patients. The series is therefore believed to be well suited for the practical trial of a therapeutic

method. Any claim of a higher average severity in any other series should be supported by definite facts and figures.

The cases are classified on a basis of purely empirical convenience, which is justified by its objectivity and a certain degree of prognostic usefulness, and which may at least serve in the absence of any accurate scientific distinctions upon which any large number of investigators can agree. This division falls into four groups, as follows:

A. *Cases of pure or "essential" hypertension with initial plasma chloride concentrations above 580 mg. per 100 cc.*— The figure of 580 mg. is chosen from the literature and from experience as representing in a crude fashion the upper normal limit of plasma chlorides. It is not the intention here to argue whether this is a true normal limit, or to deny that figures above 600 mg. may be found in supposedly normal persons, particularly after large salt ingestion. As already mentioned, the occurrence of higher figures in other diseases, lacking the organic vascular lesion which is the basis of hypertension, has no bearing upon this subject. Later careful studies must decide whether high plasma chloride figures with moderate chloride intake are actually physiological, or whether such supposedly normal individuals really have slight renal-vascular lesions or are candidates for future hypertension. For the present, the fact is simply that a large majority of cases of "pure" hypertension (73 out of 104 in the present series) have shown plasma chloride concentrations above 580 mg., not only after eating but also before breakfast. Edema in these cases is usually absent or very slight. There may sometimes be a slight swelling of the ankles during the day, or an appearance of the face which may be called "puffy" or "apoplectic" or "frog" face. Even in a patient who is supposed to be entirely free from edema, the loss of several pounds of water from the body on salt-free diet may show a visible result in less tenseness of the skin, less bulging of the eyes, and increase of wrinkles. The reason for the retention supposedly is either a high renal threshold for sodium chloride, or the ingestion of larger quantities of salt than can be readily excreted by the damaged renal-vascular apparatus. One reaction to this condition seems to take the form of elevation of blood chlorides, "dry" retention in the tissues, and high blood pressure.

B. *Cases of hypertension with initial plasma chloride con-*

centrations below 580 mg. per 100 cc. — These cases are a minority, namely, 31 out of 104 in the present series. The number would be smaller if certain disturbing influences could be excluded. For example, patients who have previously been placed on salt-poor diets, or who habitually eat very little salt, represent merely a defect in the classification, which could be avoided only by the use of standard preliminary diets. Also, in so-called "mixed" cases, hypertension may coexist with edema. When the chlorides can pass easily into the tissue spaces, they frequently do not accumulate in such high concentration in the blood. The influence of drugs will bear further study; for example, bromides and iodides are said to reduce the blood chlorides[67]. No specially bad prognosis necessarily attaches to any of the above types of cases. On the other hand, there is a small proportion of cases of so-called "pure" hypertension which show low plasma chloride concentrations not explained by any of the above modifying factors, and our experience indicates that in this group the prognosis is generally though not invariably worse than in the group with high plasma chlorides. It has not been possible to investigate the question whether the low chloride level is associated with a different type or degree of organic changes.

C. *Cases of hypertension with nephritis.* — Presumably renal lesions in some sense or degree were present in all the cases, and distinctions must be quantitative or arbitrary. The absence of any accurate or universally accepted nomenclature is understood, and the word "nephritis" is used not in an etiologic or pathologic sense, but as a brief expression for a renal disorder recognized chiefly by impairment of nitrogen excretion.

Observations of renal function in this series of cases will be reported by one of us in a later paper. For the present purpose, cases with marked Bright's disease deserve a separate grouping because of their much worse prognosis as respects both lowering of blood pressure and preservation of life. Therapeutically, also, "pure" hypertension cases require little or no restriction of protein food, and salt privation can be pushed with no fear of anything worse than the familiar privation symptoms; while the association with "nephritis"

demands limitation of protein and care in the reduction of salt and water, for guarding against uremia.

D. *Cases of hypertension with diabetes.*—The combination of hypertension with hyperglycemia, lowered sugar tolerance, slight glycosuria, or frank diabetes has given rise to a small literature, a review of which must be omitted in the interests of brevity. The present grouping is therapeutic, covering cases in which carbohydrate and total calories were restricted in addition to salt. Any long-continued hyperglycemia or subnormal tolerance has been regarded as diabetic in nature, but the causes of the frequent association of this condition with hypertension are still largely hypothetical.

Apparently to some extent diabetes conduces to arteriosclerosis, and sclerosis of the pancreatic vessels, especially of the island capillaries, may be a basis for diabetes; also, it is conceivable that injury of the pancreas at one time may give rise to diabetes, and a different agency at a different time may produce the vascular injury which gives rise to hypertension; but it seems a plausible assumption that the same infection or intoxication frequently damages the pancreas, kidneys and perhaps other organs so as to produce the entire pathologic condition. The unproved speculations concerning adrenalin as a factor in either diabetes or hypertension are not strengthened but weakened by these combined examples. If adrenal hyperfunction is concerned in diabetes, it is difficult to understand why most diabetics have normal blood pressures; and if adrenal hyperfunction plays a part in hypertension, it is difficult to explain why most hypertension patients have normal blood sugar and carbohydrate tolerance. For practical purposes, the combined cases form a convenient group because of the dietary requirements above mentioned, because the blood sugar seems to bear some relation to the blood pressure, and because the prognosis, contrary to older ideas, is generally favorable under proper treatment.

DISCUSSION OF TABLES 1 AND 2.

The favorable character of the first group, namely, "essential" hypertension cases with plasma chloride concentrations above 580 mg. per 100 cc., is evident in the proportion of only 1 dead patient and 72 living. Also, 56 of 72 patients were definitely improved and have not relapsed. It is equally noticeable that of the 17 unimproved patients, only 1 has died. The second group, comprising cases with plasma chloride concentrations below 580 mg., shows a higher proportion of deaths (5 out of 31 cases), of relapses (3 out of 20 improved cases), and of failure to benefit (11 out of 31 cases), illustrating the poorer prognosis above mentioned. The third group, of hypertension with nephritis, represents the most dangerous

TABLE 1.

Results of Treatment According to Decades of Life

A. *Cases of Hypertension with Plasma NaCl Concentration above 580 mg. per 100 cc.*

Decade of life	NO. OF CASES		TOTAL	IMPROVED		UNIMPROVED	
	Living	Dead		Living	Temporarily improved but later died	Living	Dead
3							
4	3			2		1	
5	14			12		2	
6	37	1		30		7	1
7	17			11		6	
8							
9	1			1			
	72	1	73	56	0	16	1

B. *Cases of Hypertension with Plasma NaCl Concentration below 580 mg. per 100 cc.*

3	1					1	
4	1					1	
5	6	1		3	1	3	
6	14	3		12	2	2	1
7	4	1		2		2	1
8							
	26	5	31	17	3	9	2

C. *Cases of Hypertension with Nephritis*

3	1	2			1	1	1
4	2	5			3	2	2
5	6	2		2	2	4	
6	6	4		5	3	1	1
7	2	3		2	2		1
	17	16	33	9	11	8	5

D. *Cases of Hypertension with Diabetes*

3							
4							
5	6	1		4	1	2	
6	19	1		15	1	4	
7	15	1		8		7	1
8							
	40	3	43	27	2	13	1

combination, as shown by the very high proportion of deaths (16 out of 33 cases), relapses (11 out of 20 improved cases), and failures to benefit (13 out of 33 cases). The fourth group, namely the patients with hypertension and diabetes, carry the burden of a double dietary restriction and face the possibility of relapse or death from either of their two disorders. Nevertheless, there were only 3 deaths among 43 patients, 2 of these resulting from complete abandonment of diet and only 1 from hopelessly intractable hypertension. Among the 29 improved cases, 2 relapses of glycosuria and hypertension occurred, from disregard of diet in both instances. There were no failures to clear up glycosuria, but 13 of the 43 patients failed to obtain any reduction of their blood pressure. Nevertheless, 12 of these 13 are still living.

The figures for decade of life in this table (based on the age at admission, not at onset of the trouble) show merely the well-known higher incidence in the later years. Youthful cases, which are comparatively rare and also less favorable in prognosis, have not chanced to come under our observation. The third and fourth decades were represented more largely in the group of hypertension with nephritis than in the other groups, but the worse prognosis for the nephritis group holds also for the later decades.

TABLE 2.

Results According to Duration of Treatment

Years under treatment	A. Cases of hypertension with plasma chloride concentrations above 580 mg. per 100 cc.			B. Cases of hypertension with plasma chloride concentrations below 580 mg. per 100 cc.			C. Cases of hypertension with nephritis			D. Cases of hypertension with diabetes		
	Total cases	Living	Dead	Total cases	Living	Dead	Total cases	Living	Dead	Total cases	Living	Dead
3 +	4	4	0	0	0	0	6	2	4	4	4	0
2 +	13	13	0	1	1	0	2	1	1	9	7	2
1 +	31	30	1	18	17	1	5	2	3	14	13	1
less than 1	25	25	0	12	8	4	20	12	8	16	16	0
Total	73	72	1	31	26	5	33	17	16	43	40	3

Table 2 analyzes the total mortality of the series with reference to the number of years under treatment. It is most important for showing that the failures and fatalities are not a mere matter of time or downward progress. In view of the fact that any group composed of middle aged and elderly persons must show an increment of death rate with the passage of more years, the favorable figures for patients observed two or three years or longer are very satisfactory. In our experience, success or failure is governed preeminently by the character of the case. Some cases are wholly or partially refractory, supposedly because the organic changes are too extreme to permit of successful treatment by functional relief. When satisfactory relief is once attained, it may generally be expected to continue so long as the diet is accurately followed and infections or other accidents are escaped. It seems needless to emphasize the fact that most of these patients have advanced renal or general arteriosclerosis, which cannot be removed by treatment and which leaves them constantly subject to the danger of fatal accidents.

DISCUSSION OF TABLES A, B, C, D.

Tables A, B, C and D summarize the details of the individual cases in the respective groups. The following may be remarked concerning the findings shown in the successive columns in all four tables.

1. Sex.—It is traditional that hypertension is far more common in males than in females. The following summary shows curious variations between the different groups in this series:

TABLE 3.

The sex of hypertension patients

	A. With chlorides above 580 mg.	B. With chlorides below 580 mg.	C. With nephritis	D. With diabetes	TOTAL
Male	33	24	24	8	89
Female	40	9	7	35	91

There was formerly an erroneous belief that diabetes is more

prevalent in the male sex. The present series is inadequate to decide whether men are more subject to hypertension, as supposed, or whether this supposition, like the former belief concerning diabetes, has been based upon inadequate examinations and upon the smaller number of women examined for hospital admission, life insurance and the like. This series may be weakened in its general statistical value by the fact that it is compiled not from the population at large but only from patients coming to an institute on account of the known existence of either hypertension or diabetes.

2. Treatment before admission and judgment of methods.— With few exceptions, these patients had received treatment previously from one or several physicians, and either came of their own choice, or in the great majority of instances were sent by their physicians to the Institute because of the failure of the previous treatment. Practically all of the standard methods are represented in the list. Convenience will be served by expressing here the judgments formed from the records of these patients, and also our own use of and attitude toward these methods.

(a) Protein limitation. — No patient in this series had obtained lowering of blood pressure from these restrictions, and several had been weakened by injudicious extremes in this direction.

(b) Milk diet and undernutrition. — These may be classed together, as measures which have an undoubted temporary value in some cases, probably because of the limitation of chloride intake involved. Their prolonged use would mean starvation, unless quantities of milk should be taken which would be harmful through both chloride and fluid excess. Being relics from a more primitive time, these methods are inferior in accuracy and efficacy to the more modern plan of chemical tests to show the condition present and dietary prescriptions to meet individual needs.

(c) Bed rest is a palliative or emergency measure, useful in threatened apoplexy, pulmonary edema or similar crises. Its use and benefit are both temporary, and it tends to make invalids of the patients. Salt-free diet has often relieved the pressure and accompanying symptoms in cases in which rest treatment has failed, but we have never seen any important relief by means of rest in cases in which salt restriction had failed.

(d) Bleeding, properly employed, is one of the most valuable emergency measures. It ranks below chloride restriction in effectiveness, and has failed even for emergency use in the cases refractory to diet.

(e) Spinal puncture. — Authors describe this as a valuable emergency measure in "eclamptic" states, when the pressure of the spinal

fluid is often found high. We have used it only in a few cases which were refractory to the strictest diet, and have never found the spinal fluid pressure high and never obtained the slightest benefit. The observations of others on cases thus treated will be of interest. As there are states of general or local hydrops which are not cleared up by salt privation, a similar condition may sometimes hold for the spinal fluid. It is possible, however, that in many cases the choroid plexus is stimulated by salt to an over-secretion of spinal fluid, and that the excessive pressure of this fluid is therefore relieved by salt-free diet. In the most severe cases, headaches and convulsions apparently can result from true brain edema, without increased spinal fluid pressure. Both spinal puncture and salt-free diet may then fail.

(f) Decapsulation of kidneys. — There was no experience with this in any of our cases. Volhard and other writers consider it valuable for anuria in acute nephritis, though still others are doubtful; and it holds no possible place in the treatment of chronic nephritis, unless for suppression of urine from some transitory intercurrent cause.

(g) Drugs. — Cardiac stimulants probably hold first place. Digitalis is commonly used to drive a heart which is failing against a hopelessly heavy resistance, and it is obviously better to reduce the resistance by diet. In a crisis, when digitalis has failed, salt privation is sometimes surprisingly prompt and powerful in enabling the drug to take effect. We have generally been able to discard heart stimulation altogether, but with either valvular defects or a seriously weakened myocardium occasional courses of digitalis or similar drugs may be desirable even after successful control of the blood pressure by diet.

Vasodilators have been widely abused, and are probably only really useful (in such forms as nitroglycerin or amyl nitrite) for acute crises such as angina pectoris. They sometimes give relief of distressing symptoms even in cases in which diet has failed, but such relief has always been brief and slight, and in extreme cases the largest doses have sometimes not altered either the pressure or the symptoms. Benzyl benzoate has been tried only in severe cases and has never given the slightest benefit. This experience is in keeping with the belief that hypertension is not a spasmodic vasoconstriction.

Opiates, chloral, and sedatives of all kinds may serve an occasional emergency purpose, as in apoplexy or angina, and may soothe the brief terminal period of entirely hopeless cases.

Purgatives, especially of the milder kind like cascara, are sometimes needed to correct constipation, which may show its harmful effects in more or less elevation of pressure and also headaches and other symptoms. They may be all the more necessary because of the constipating effect of salt-poor diet in some patients, which may not be sufficiently counterbalanced by laxative foods or the use of mineral oil or bran. Violent purgation with Epsom salts, etc., has been required only for specially stubborn constipation, particularly in patients who had been previously treated by such purgation daily over long periods. In severe cases, more or less refractory to diet, we have never seen the slightest benefit from drastic daily purging, used in the attempt to

wash out either additional quantities of salt or imaginary toxins. We have never tried intestinal irrigations of any kind, but the reports of patients who had previously received such treatment never indicated any benefit. It is chiefly important to avoid introducing salt by these measures. If salts are used for purgation, they should be of some pure, poorly absorbable kind, as magnesium sulphate, etc., not mineral waters or effervescing or other mixed salts containing chlorides or anything convertible into chlorides. One patient who had responded well to diet experienced a return of symptoms after going home, and the 24-hour urine sample showed 4 gm. of sodium chloride not accounted for by his diet. It was then learned that he had been giving himself high enemas of salt solution, to which he had become accustomed before entering the Institute. The stopping of these relieved his hypertension and other symptoms.

We have never used any diuretic drug in any hypertension case, with or without nephritis. The principle of treatment is to avoid putting harmful substances into the body, rather than putting them in and then trying to force the damaged kidneys to excrete them. It is an open question whether in so-called "nephrosis" or other forms of renal disease diuretics will ever accomplish anything which exact diet cannot accomplish. Generally, at least, they do not, and there is danger of actual injury of the kidneys by such drugs. Especially is this to be feared from mercurials such as calomel and from all the more violent diuretics.

Iodides and all other supposed specifics for hypertension or arteriosclerosis lack any demonstrated value. This discussion obviously does not pertain to the treatment of any underlying infections, such as syphilis. Iodides, bromides and some other compounds are credited with an influence in reducing blood chlorides and increasing chloride elimination. We have made a slight investigation of these other halides and also potassium salts for this purpose and as partial substitutes for sodium chloride in the diet, but nothing of any therapeutic usefulness has developed thus far.

In general, we believe that only a few drugs have a purely temporary and symptomatic usefulness for emergencies. Continuance of such symptomatic treatment does not reach the cause of trouble or alter the real condition. For example, the routine use of nitrites can give only misleading symptomatic results at best, and should be replaced by a causal therapy.

(h) Physicotherapy. — More or less reduction of blood pressure and relief of subjective symptoms are credited to various forms of hydrotherapy, mechanotherapy or massage, various applications of heat, high frequency electricity, and other physical devices. We have gone to an extreme in using none of them whatever. Judging from the records of patients, such treatments give only temporary and symptomatic benefits in some of the milder cases, far inferior to the results of salt restriction, and they have never accomplished anything in cases in which diet has failed.

(i) Climate and resorts. — A slight excretory function is attributed

to the sweat; also, warmth of the skin surface is supposed to favor renal activity and general vascular relaxation. Numerous patients feel distinctly worse on cloudy or stormy days, and better on clear sunny days. Physicians have long been accustomed to send patients to resorts where the environment is supposed to be somehow beneficial. On the other hand, we have obtained only weakening effects and no benefit from attempts to sweat out salt in difficult cases. Successful results of diet treatment make change of climate unnecessary, and such a change has never added to them. The alleged benefits of mental relaxation in resorts are only temporary and symptomatic, and are offset by the invalid habits thus fostered. A normal vacation under conditions of accurate diet is better. Patients who have gone to various climates and resorts after failure of the diet treatment have not been benefited. In actual practice, we have obtained entirely similar results winter and summer, and have never advised any patient to take a trip, either for the sake of a supposedly helpful environment or for escaping the responsibility of our failure.

(j) Removal of infectious foci. — This method is on a different plane from the others mentioned, because it is an attempt to eliminate the primary cause of hypertension. Doubtless the search for such foci has been carried to too great extremes by some physicians, and many inoffensive teeth and tonsils have been removed. Nevertheless, any genuine source of infectious or toxic injury, whether an old syphilis or a pus pocket, may be viewed in the same way as in diabetes, namely as either the original cause or at least an aggravating influence, and a cure by suitable medical or surgical means may be expected either to help the constitutional disorder directly or at least to aid in arresting its progress. We have seen one instance of early hypertension apparently cured by tonsillectomy, but such complete success will doubtless be found chiefly in incipient cases like this one, rather than among the more severe and chronic types which compose this series. In the latter class, as in corresponding diabetic cases, it must be considered that removal of a primary focus still leaves behind the results of organic injury, and functional rest of the damaged organs is therefore necessary. It may be a defect in our methods that we have not searched more minutely for infectious foci in this series of cases.

In summary, we share the opinion of a large part of the medical profession that very little is accomplished by the prevailing methods of treating high blood pressure. Many physicians, regarding the pressure as a mere symptom or perhaps as compensatory and useful, prefer to refrain from meddling with it. Janeway[38] wrote, "Hypertension is no more to be attacked therapeutically than a heart murmur". We sympathize with this view unless a treatment can be directed at the cause.

3. *Duration.*— As the onset of hypertension, like that of

diabetes, is in the great majority of cases either gradual or uncertain, the figures for duration are necessarily widely inaccurate. The records in tables of this sort can give only the periods during which hypertension has been definitely known to exist according to some physician's diagnosis. The time stated therefore must be in the majority of cases considerably less than the actual duration. Even on this basis, the great mass of these cases are demonstrated as firmly established and chronic in type. The stress laid in some medical writings upon variations with time of day, psychic influences, and other accidental factors creates the impression that these authors are dealing with the earlier or milder types of hypertension. The patients who have the most serious symptoms and who cause the greatest worries to practitioners are those who may indeed have their symptoms and pressures increased by various transitory disturbances, but who are never free from distress and never show pressures below 200 or some

TABLE 4.

Body Weight of Patients

BODY WEIGHT	A. Cases with plasma chlorides above 580 mg. per 100 cc.		B. Cases with plasma chlorides below 580 mg. per 100 cc.		C. Cases with nephritis		D Cases with diabetes		TOTAL		Grand total
	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved	
Above standard normal	31	11	10	4	2	3	7	9	50	27	77
At or below standard normal	21	4	8	7	15	9	18	6	62	26	88
Reduced under treatment	44	11	16	7	17	8	28	12	105	38	143
Not reduced under treatment	12	5	4	6	2	4	2	1	20	16	36
Reduced more than 2 kg.	24	8	9	2	15	3	22	7	70	20	90

other abnormal figure. When patients with records of this character and duration have their symptoms relieved and their pressure kept consistently below their former minimum limits, the results have objective scientific value as a basis for conclusions.

The next column shows the number of months of observation of the respective cases under treatment. In a high proportion of instances, this is long enough to indicate the permanency, and as the results are practically identical in the shorter and longer periods, the degree of success can thus be fairly judged.

4. *Body weight.* — An analysis of the observations from certain standpoints is contained in Table I. The standard normal weights are calculated from the height-weight formula of the Association of Life Insurance Directors and Actuarial Society of America (New York, 1912, pp. 38 and 67).

No separate tabulation has been made of the highest weights in the patients' lifetimes, because the great majority of the hypertension patients have not been undernourished and the admission weight is also the maximum weight. Some exceptions are found in the nephritis series (Table C), due to cachexia in several cases, but edema creates a greater disturbance of accuracy in the opposite direction. The subnormal figures in Table D were due chiefly to loss of weight with diabetes, most of the patients having been overweight at the onset of their diabetes, but this relationship has been sufficiently shown by Joslin[68] and confirmed in our former publications[69, 70]. The data demonstrate two facts.

First, as opposed to the great stress placed by most writers on obesity in connection with hypertension, the majority of these patients (88 out of 165 cases in which the height is known) have been normal or slightly subnormal in body weight. The majority of the "pure" hypertension cases (groups A and B) were slightly or moderately overweight. Instances of great obesity are rare in this series, and it may be added that the majority of obese patients seen in this Institute have not had hypertension. The complication is therefore probably an accidental one, like the complication of hypertension with diabetes, though it need not be doubted that obesity as well as diabetes may somewhat increase any existing tendency to hypertension.

Second, the treatment and its results have no connection with the state of nutrition. In the first place, it is to be noticed that improvement and lack of improvement were encountered both in patients who were above normal weight and in those who were below normal weight at admission, and in proportions which varied accidentally

with the severity of the cases rather than with the nutritive state. In the second place, improvement and its absence were found both in patients whose weight needed reduction and was reduced under treatment, and in those whose weight did not diminish or sometimes slightly increased. From a mere summary showing reduction of weight under treatment in 143 cases and absence of reduction in 36 cases, it might be hastily inferred that undernutrition was a usual feature of the treatment. Examination of the detailed tables (A, B, C, D) will show that the loss of weight was commonly no more than 1 or 2 kg., which is easily within the limits of water loss by patients of this type on salt-poor diets. A further reckoning then shows that only 90 out of 179 patients were reduced by more than 2 kg. If allowance be made for the number of cases in which more than 2 kg. of edema fluid was lost, it becomes evident that only a minority of the total number of patients were actually reduced in bodily tissue. Further comparisons of the therapeutic results show that the degree of success in patients reduced by more than 2 kg. is by no means above the general average for the series. Nevertheless, a comparison of the entire group of 143 cases reduced in weight with the entire group of 36 cases not reduced in weight shows a distinct advantage for the former. The explanation of the difference is twofold. First, a slight benefit to hypertension is recognizable from removal of the slightly aggravating influence of obesity, above mentioned. In the milder or earlier forms of the disorder, therefore, pressures which may sometimes be decidedly high may be reduced nearly or quite to normal by the reduction of obesity alone; but in more severe and firmly established cases, such as the majority in this series, undernutrition fails to achieve this success, as shown by the lack of any strikingly better average results in the patients who were reduced by more than 2 kg. Second, the most important basis of difference is found in the loss of water and salt from the body. This is comparable in a general fashion to the different prognosis connected with high and low plasma chloride levels, in the absence of special disturbing influences. When there is much salt retained in the blood and in tissues turgid with edema, especially of the "invisible" type, the loss of one to several kilograms of water on salt-poor diet is generally accompanied by the greatest benefit to the hypertension and its attendant symptoms. On the other hand, patients who have retained little salt or fluid and who accordingly lose little on salt privation, are apt to be correspondingly little influenced in their condition.

The entire data therefore support the conclusion that obesity is not a primary cause of hypertension and that undernutrition is not the means by which either success or failure has been determined in this series.

5. *Plasma chlorides.*— Chloride analyses were performed on the plasma of oxalated blood by Whitehorn's method[71].

Control tests, which will be published later if necessary, have been opposed to the idea[72, 73] that any important changes occur within the

time necessary for centrifugation and separation. The chlorine content of the corpuscles, like their sugar content, is still a matter of some dispute, but is generally considered to be slightly below that of the plasma. Furthermore, to a large extent the chlorine compounds of the corpuscles are believed to differ from those of the plasma chemically and biologically.

Further studies of the interchanges of chlorine between corpuscles and plasma will be of interest, though not necessarily running parallel to similar interchanges between the plasma and the body cells in general. For the present purpose, however, it must be considered that only the chlorides of the plasma come into direct relation with either the kidneys or other tissue cells, and serious discrepancies can be introduced by the varying proportions of corpuscles in nephritis and hypertension cases, ranging all the way from marked polycythemia to extreme anemia. For these reasons it is surprising that Mosenthal and O'Hare have undertaken to base their comparisons upon the inherently unreliable plan of whole blood analyses. Circulatory conditions, including the stasis used in taking the blood sample from the vein, doubtless modify somewhat the chloride content of both plasma and corpuscles. As all the possible changes, *in vivo* and *in vitro*, appear to affect both the chloride and the bicarbonate, it is highly probable theoretically that the same precautions will insure for chloride analyses a reliability equal to that of the bicarbonate analyses, which are regularly performed upon the plasma.

The largest diurnal variations of chlorides occur in the form of increases after salt ingestion and decreases after water drinking. These discrepancies were guarded against by taking blood samples in the mornings before breakfast. Doubtless the influences of diet, diuresis, drugs, etc., are not thus entirely excluded, but it seems doubtful if strictly normal individuals on moderate salt rations ever show higher plasma chloride concentration than 580 mg. per 100 cc. under these conditions. If this assumption be correct, the finding of higher concentrations than this in a large proportion of hypertension cases is significant in itself. The largest of the four groups, comprising 73 patients, was segregated on this basis. Plasma chlorides above 580 mg. were also observed in 17 of the 31 cases of hypertension with nephritis, and in 18 of the 43 cases of hypertension with diabetes. Accordingly, retention of sodium chloride above the limit assumed as normal was encountered prior to treatment in 108 out of the total series of 180 cases. The highest value observed was 659 mg. per 100 cc.

Renal function tests, showing that the renal threshold for chlorides as calculated on Ambard's principle is also above

normal in the great majority of the cases, must be reserved to a later paper. Ambard himself, however, recognized that this threshold may be changeable, and it is a frequent experience that with salt-poor diet the plasma chloride concentration may be brought considerably below the theoretical threshold. A comparison of this series of cases on the basis of the plasma chloride concentrations finally attained shows the following:

TABLE 5.

Changes in Plasma Chloride Concentrations Under Treatment

Final Plasma NaCl Concentration	A. Hypertension with plasma NaCl above 580 mg. per 100 cc.		B. Hypertension with plasma NaCl below 580 mg. per 100 cc.		C. Hypertension with Nephritis		D. Hypertension with Diabetes		TOTAL		Grand total
	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved	Improved	Unimproved	
At or above original level	11	5	13	9	7	5	9	3	40	22	62
Below original level	47	8	8	4	10	9	17	8	82	29	111
Above 580 mg. per 100 cc.	27	7	6	1	4	5	8	3	45	16	61
At or above 560 mg. per 100 cc.	50	11	14	7	7	9	20	7	91	34	125
Below 560 mg. per 100 cc.	8	3	7	5	10	5	6	4	31	17	48

Of the 173 patients represented in Table 5, 58 received final NaCl rations of 1 to 3 gm. per day, while 6 others received larger amounts up to 10 gm. The remaining 109 patients continued on strict "salt-free" diets. Our experience with normal individuals leads us to believe that a marked and prolonged reduction of their chloride intake results in a distinct lowering of the plasma chloride level; also, that the strictly normal person on minimal salt intake has a plasma chloride

concentration never above 580 mg. and seldom if ever above 560 mg. per 100 cc. It will be noticed in Table 5 that the plasma chlorides under treatment fell below the original level in 111 of the 173 cases, but were unchanged or rose above the original level in 62 cases. Furthermore, in 61 cases the concentration remained above 580 mg., and in 125 cases above 560 mg., and fell below 560 mg. in only 48 cases.

We have at no time held or expressed the opinion that the blood pressure of either normal or hypertensive individuals varies in parallel with the plasma chloride concentration. Table 5 shows that therapeutic successes and failures were obtained practically indiscriminately, whether the plasma chlorides rose or fell. The class of cases in which the plasma chlorides were reduced below 560 mg. per 100 cc. showed the poorest result of all, namely, 17 failures among 48 cases, for the reason that the initial chloride concentrations in most of these cases were also low and the prognosis correspondingly poor, as already mentioned. In individual cases also, the degree of reduction of blood pressure by no means corresponded to the changes in the plasma chlorides. The diabetic group (Table D) contains two striking illustrations. In case 140, salt-free diet reduced the plasma chlorides from 624 to 565 mg. per 100 cc., but the blood pressure fell only from 195/115 to 188/100, and this improvement has been difficult to maintain in the presence of marked arteriosclerosis. In case No. 1066, the plasma chloride concentration rose from 564 to 612 mg., while a rapid and lasting reduction of blood pressure occurred, from 180/100 to a normal level of 130/75. Many similar examples in all the four groups of cases prove the same rule. The variations are sometimes explainable by the increase of plasma chloride concentration attending the clearing up of visible or invisible edema, or diminished water drinking on salt-poor diets, etc., but to a still greater extent they must be ascribed to the entirely unknown laws governing the distribution of salts between cells, tissue fluids, blood stream and urine.

6. *Blood urea.*— Normal blood urea concentration on a liberal protein diet is probably as conclusive as any other simple test as an indication of an adequate function of nitrogen excretion. It will be seen that this relation holds in a general way for groups A and B, and also for group D with

the exception of a few cases in which a mild nephritis accompanied the diabetes. These observations harmonize with the generally accepted view that retention of urea or nonprotein nitrogen bears no relation whatever to vascular hypertension. In general, also, the kidneys of these patients react normally in their ability to prevent any serious accumulation of waste nitrogen when salt is withdrawn from the diet. There is no doubt that the diminished diuresis resulting from reduced salt and water intake imposes a harder task upon the kidneys in this respect. Whenever the blood urea has tended to rise above a figure that seems theoretically desirable, we have either restricted the protein intake slightly or advised the patient to drink a little more water. These simple measures have allowed the salt privation treatment to be carried out smoothly without any disturbance on the side of nitrogen elimination, as the tables show.

A different condition is encountered in the nephritic cases in Table C. Here the blood urea values either are abnormally high, or have been kept down by low protein diet either before or after admission to the Institute. High creatinin figures, not included in the present report, were frequent even in the latter class. It will be observed that the salt-poor diet has ordinarily been carried out successfully in this group of cases, without serious increase and sometimes with a considerable reduction of nitrogen retention. This result has been accomplished chiefly by strict limitation of the protein allowance. Patient No. 11, for example, with an exceedingly severe combination of diabetes, nephritis and heart disease, was kept fit for light work for long periods on 30 gm. protein per day, as shown in his previous published record[74]. Nevertheless, in severe cases danger may result from a sudden withdrawal of salt. Patient No. 90, for example, developed alarming uremic symptoms when first placed on salt-free diet, and was quickly relieved by the giving of 10 gm. of sodium chloride daily. It was necessary to ignore his hypertension until a very low protein regime had been followed for a number of weeks. It was then possible gradually to reduce the salt intake so as to relieve the edema, hypertension and cardiac failure, and improve the general clinical condition greatly. On account of this danger, it is inadvisable to impose salt-free diets except under ac-

curate laboratory control, or, if this is actually not obtainable, at least under close clinical observation.

In severe and progressive cases of nephritis, the urea retention may increase in spite of diets free from salt (cases No. 13, 90, 377, 434) or containing salt (cases No. 978, 521, 1090, 2107). In these and other cases of Table C it will be observed that the fall or rise of blood pressure is entirely independent of the increase or decrease of urea retention. It will be shown also, in illustrative case histories (Part II) that the changes in blood pressure are influenced by the chloride ration but not by the protein ration. Further evidence is thus afforded that the blood pressure is independent of protein ingestion or nitrogen retention.

7. *Albumin and casts.*— The tabulated experience with this series of cases conforms to the general rule that careful examination will demonstrate albumin and casts at least in small amounts in the urine of the great majority of patients with hypertension. This is one suggestive indication that the kidneys are concerned in this condition. The occasional absence of albumin or casts, or both, obviously does not exclude a disorder of the kidneys or their vessels, according to present views of renal pathology. In the majority of cases the albumin and casts remain unaffected by the treatment or the reduction of blood pressure. In a minority of instances, however, chlo-

TABLE 6.

Summary of Plasma Sugar Findings.

Plasma sugar concentration	A. Hypertension with plasma NaCl above 580 mg. per 100 cc.	B. Hypertension with plasma NaCl below 580 mg. per 100 cc.	C. Hypertension with Nephritis
Below .12%	26	8	3
Between .12 — .15%	28	13	7
Between .15 — .20%	11	8	10
Between .20 — .25%	0	1	2
Total	65	30	22

ride restriction has unmistakably reduced albumin and casts, and in a few cases they have disappeared from the urine. This statement is based upon a sufficient number of observations both before and after treatment, in established chronic cases, to exclude accidental variation. These results, when obtained, are probably one sign of improvement in the renal and general circulation.

8. *Plasma sugar.*— Excluding definitely diabetic cases, the observations of plasma sugar in this series are shown in Table 6.

Assuming 120 mg. per 100 cc. as the upper normal limit of plasma sugar before breakfast, it is seen that 80 out of 117 patients with hypertension, or 68.3 per cent, had hyperglycemia at admision. In general, the statistics for hyperglycemia stand in inverse relation to the clinical prognosis. Thus, in group A, in which the therapeutic results were best, the plasma sugar was normal in 26 of 65 cases, or 40 per cent. In group B, in which the average success of treatment is lower, the plasma sugar was normal in 8 of 30 patients, or 26.6 per cent. In group C, comprising the most dangerous cases, the plasma sugar was normal in 3 of 22 cases, or 13.6 per cent. These general relations, however, do not hold good when applied to individual cases, and are completely overturned in the cases of outright diabetes.

These analyses were all performed with Benedict's method, which yielded consistently normal figures in healthy persons and in diabetic patients under suitable treatment. Hyperglycemia was often found in patients without urea or creatinin retention. In a number of instances, the filtrate from the picrated plasma was further cleared with charcoal according to Benedict's suggestion; also, in the majority of the nephritic cases, the results were further checked by parallel analyses with the method of Folin and Wu. These procedures yielded only slightly lower figures and confirmed the existence of marked hyperglycemia. Furthermore, all patients with any important hyperglycemia have as a routine been subjected to glucose tolerance tests, which have indicated decided lowering of carbohydrate assimilation. For these reasons, it is believed that the hyperglycemic figures tabulated represent actual blood sugar rather than interfering substances.

The interpretation of high blood sugar values with cerebral hemorrhage or certain forms of so-called "uremia" is uncertain, and they may possibly be due to nervous irritation or other causes. For this reason, case No. 2013 in group C, with plasma sugar of 319 mg. per 100 cc., has not been classed as diabetic, though the possibility of diabetes is open. In general, it seems most plausible to correlate the

frequent hyperglycemia of hypertension cases with the arteriosclerosis and fibrosis of the pancreas which are also frequent in such cases. The view that these findings represent actual diabetic tendencies, ranging all the way from the slightest impairment of assimilation to genuinely severe diabetes, is supported by two-fold evidence: first, the results of glucose tolerance tests, above mentioned; second, the response to diabetic diets. The widespread belief in a peculiarly refractory character of the hyperglycemia with hypertension or nephritis has not been substantiated in our experience. It is true that in certain exceptional cases there may be marked hyperglycemia which seems almost impossible to reduce, and yet glycosuria may perhaps never have been known, other diabetic symptoms may remain absent, and no progressive tendency may be evident. Glycosuria in these cases may be somewhat impeded by the high renal threshold for sugar, but all the other peculiarities mentioned are exactly duplicated in some long-standing mild diabetic cases in later life without hypertension or nephritis, in which hyperglycemia may have existed for ten to thirty years with only slight harm or progressiveness. The misconceptions concerning chronic hyperglycemia with nephritis, which have caused adrenalin and other imaginary agencies to be dragged in for attempted explanations, have been due chiefly to ignorance of two things: first, the extreme stubbornness of blood sugar elevation in many cases of mild diabetes of extremely long duration, irrespective whether hypertension or nephritis is present or not; and second, the fact that control of the blood sugar requires regulation not only of carbohydrate but also of fat, total calories and body weight. In general, diabetic patients with hypertension or nephritis respond to diabetic treatment in the same manner as patients with similar types of diabetes without these complications.

Hyperglycemia of trivial degree has been ignored in our treatment. The more pronounced grades have been treated so as to reduce the blood sugar and to keep it normal, if this could be accomplished without too extreme privation. Reduction of weight was often the chief requirement. The treatment of the renal or vascular condition and the treatment of the diabetes create no conflict or difficulty, except that the patient may have to endure additional privations of diet; for example, in certain nephritis cases there may be restriction of salt and also sharper limitation of protein than is demanded by diabetes alone. This combination taxes chiefly the skill of the dietitian, and with the variety of natural and artificial foods and flavors that are still available it is possible to make diets sufficiently pleasing that very few patients in this series have trangressed them. The prognosis of the case is generally determined by the single condition which is most dangerous. This is not aggravated by the co-existing disorder, nor is the expectation of life shortened thereby. While unchecked diabetes seems to dispose to arteriosclerosis and hypertension, in cases in which the essential basis of these disorders is present, on the other hand control of the diabetes seems often to aid in reducing the blood

pressure. For example, some hypertension cases of rather mild type (though the actual systolic and diastolic readings may be decidedly high) are partially or completely relieved of their abnormal pressure merely by diabetic diet which reduces their excessive blood sugar. Though obviously hopeless severity of hypertension or nephritis may coexist with diabetes, the average prognosis for such combined cases under treatment is good, because improvement is favored by two agencies, namely, reduction of salt and reduction of sugar. Granting that diabetes sometimes arises from sclerosis of the pancreatic vessels, it has not yet been observed that the better circulatory conditions resulting from salt restriction have improved carbohydrate assimilation, though the tendency to gangrene and similar accidents is presumably reduced. For these reasons strict treatment of each of the conditions present is considered advisable in these combined cases.

9. *Blood pressure.*— As already mentioned, the figures for blood pressures represent not single observations but a sufficient number to exclude accidental fluctuations. The initial pressures shown are minimal rather than maximal; in particular, it was known from the histories that many of the patients were subject to attacks in which the blood pressure rose much higher than the figures shown, but it was intended that these figures should represent either the minimum or the habitual blood pressure of each patient as observed both by ourselves and by the family physician. In a sufficient proportion of the cases the chronic and confirmed character of the hypertension is established by records which exclude any supposition that the changes occurring under treatment may be due to accidental or spontaneous remissions.

The column showing the pressures after treatment also represents not single or specially favorable observations, but the levels at which the blood pressure could consistently be held by means of the diet. Institutional environment is not involved, because, though the improvement recorded was generally obtained prior to discharge, in some instances the results were incomplete at discharge and the maximum and lasting benefit was achieved only after several months of further careful diet at home. It will be noticed that in successful cases there was a fall not only of the systolic but also of the diastolic pressure; generally, however, the latter was more stubborn and was reduced to less extent than the former. The pulse pressure was commonly somewhat less after treatment than before. In only 34 cases (18.9 per cent) was there a reduction of blood pressure to strictly normal levels. This incomplete

result of functional relief by diet is believed to be due to the severe and organic character of the cases comprised in this series. The evidence of benefit consists not only in the lower blood pressure readings, but still more in the transformed state of the patients as respects comfort, activity, and capacity for usefulness.

10. *Length of treatment.*— The periods mentioned in this column represent the time required to accomplish the reduction of pressure shown in the preceding column. The most favorable cases generally respond in the shortest time, so that the pressure sometimes falls completely to normal within a few days. Many unnecessary failures, however, will be made by physicians who abandon the treatment after too short a trial. As already mentioned, more or less complete success may be attained only after several months of strict institutional or home treatment. The longest period required was approximately one year. The differences pertain both to the salt retention and to the symptoms. Apart from cases of marked edema, it is a general rule that patients with large salt retention receive greater benefit than those whose retention is small, but exceptions are encountered. Also, the stubbornness of the retention varies independently of the quantity; either large or small stores of salt in the body may require from a few days to a few weeks for their elimination. The symptoms are similarly variable. Subjective relief is often experienced before the blood pressure has fallen appreciably, indicating that the mere mechanical elevation of pressure is not the chief cause of the distress. A number of other patients are only incompletely if at all relieved of their pressure and symptoms as long as any considerable quantity of retained salt continues to appear in the urine. Still others complain of their usual discomforts for longer or shorter periods after the urine has been nearly freed from chlorides. Evidently in these cases an appreciable duration of functional relief is required before the circulation improves sufficiently to clear up the symptoms. A minority of cases, as mentioned, in which organic changes are supposedly too far advanced, receive little if any perceptible benefit from even the strictest and most prolonged dieting, and these are openly confessed as partial or complete failures. Inasmuch as salt restriction is harmless, when intelligent precautions are taken against privation symp-

toms or uremia, we have felt that apparently refractory cases should receive the benefit of the doubt by being kept indefinitely on the program that has proved beneficial to others. Not only may acute exacerbations and accidents of serious or fatal nature thus perhaps be warded off for some length of time, but a few cases in which acknowledgment of failure had been made to the patient and family have finally turned definitely for the better.

11. *Final chloride ration. Food tables.*—As already mentioned, the diet was regarded as "salt-free" for the present purpose when the sodium chloride content of the urine was kept at or below 0.5 gm. per day. To accomplish this purpose, foods of very low salt content must be chosen, and no salt is added. Experiments have been made in difficult cases by using distilled water and boiling out the natural salts of foods, so as to keep the urine for some time completely free from chloride; but no greater clinical benefit has thus been accomplished to offset the greater danger of privation disturbances.

Three points regarding the salt ration should receive notice.

First, 109 out of the entire series of 180 cases have been kept continuously on the "salt-free" diet yielding no more than 0.5 gm. of urinary chloride. According to present information, few if any normal persons could endure such diets for such lengths of time without privation symptoms, and the ability thus to endure these diets without symptoms is evidence of an abnormality of chloride metabolism in these hypertension patients.

Second, omitting the 6 cases in which 5 to 10 gm. of sodium chloride were given as a precaution against uremia, there remain 58 patients who received 1 to 3 gm. of NaCl per day, either because these quantities were required to ward off privation symptoms or because they could be permitted without retention or rise of blood pressure. Accurate rationing of salt is essential to success in severe cases. In most instances the "salt-free" diet was continued, and the patient each morning received the weighed quantity of extra salt which he was free to use at his discretion throughout the day. It can readily be shown that in the worst cases 1 gm. of salt per day is too much, and causes a rise of plasma chlorides and a return of hypertension and other symptoms. In other cases 1 gm. per day may be necessary to prevent privation symptoms and may be borne safely, but 2 gm. results in retention and rise of blood pressure. The intolerance of these patients for such small quantities of salt is the strongest demonstration of abnormality in their chloride metabolism.

Third, the strictness of the above requirements furnishes a sufficient explanation of many failures in the use of salt-free diets. Mere advice to an office patient to refrain from using salt is hopelessly inadequate,

and the so-called "salt-free" diets of most hospitals contain enough chloride to prevent success in the more severe forms of hypertension. A primary necessity is to have salt-free diets prepared in a sufficiently appetizing manner that patients can follow them for months and years without disgust, and failure to master this simple art has resulted in some disappointments. Fixed recipes are not employed, because each diet must be suited to the taste of the individual patient. The imagination of the cook should suggest a multitude of seasonings and flavorings other than salt. One of the greatest difficulties is that physicians are too prone to regard a salt-free diet as a very simple matter, whereas it is very exacting. Reports of experiences with salt-free diets are worthless as evidence unless they are checked up by analyses of the daily chloride output. Institutional treatment is fully as important for hypertension as for diabetic patients, in order that the chloride tolerance may be studied, a satisfying diet be planned with a view to this and any of the frequent complicating conditions, and a knowledge of the diet and fidelity to it be inculcated. Under favorable conditions of accuracy this program is sometimes successfully carried out at home, especially if a dietitian be employed for the purpose, thus proving that the mere institutional atmosphere is not the important factor. After the initial period of observation and instruction, treatment is continued on the basis of occasional office calls (usually several months apart in successful cases, more frequently in the more dangerous cases) for reports, blood pressure readings, blood analyses, and analyses of the 24-hour urine samples.

In response to numerous inquiries, a table of sodium chloride percentages of foods, copied from Friedenwald and Ruhräh's textbook, is here included, together with two sample diets, and recipes for cornstarch cookies and fudge, as examples of foods high in calories and low in both salt and protein.

SODIUM CHLORIDE CONTENT OF FOODS

From Friedenwald and Ruhräh

MEATS	NaCl %
Frogs' legs	0.05
Rabbit	0.085
Lamb	0.09
Pork, lean	0.10
Beef, lean	0.11
Veal	0.13
Calves liver	0.14
Mutton	0.17
FOWL	
Chicken	0.14
Duck	0.14
Turkey	0.17
FISH	
Eels	0.021
Salmon	0.061
Pickerel	0.077
Carp	0.086
Pike	0.092
Perch	0.100
Salmon trout	0.120
Cod fish	0.166
Mackerel	0.210
Halibut	0.310
Haddock	0.390
EGGS	
Duck eggs	0.13
Goose eggs	0.14
Hen eggs	0.21
Hen eggs (yolk)	0.039
FRUITS	
Plums	0.0045
Damsons	0.0046
Apricots	0.0047
Oranges	0.0057
Strawberries	0.0100
Watermelon	0.0110
Cherries	0.0130
Grapes	0.0240
Pineapple	0.0710
Currants	0.0930

MILK AND CREAM, BUTTER	NaCl %
40% cream	0.45
20% cream	0.55
16% cream	0.60
Whole milk	0.75
Salt-free butter	0.02-021
BREAD, CEREALS, ETC.	
Salt-free wheat bread	0.18
Oatmeal	0.014
Quaker oats	0.082
Rolled oats	0.350
Macaroni	0.067
Rice	0.039
Hominy grits	0.29
SUGAR AND CHOCOLATE	
Raw sugar	0.11
Lump sugar	0.049
Chocolate	0.073
VEGETABLES	
Carrots	0.016
Onion	0.09-0.016
Artichokes	0.036
Asparagus	0.040
Cauliflower	0.050
Rhubarb	0.059
Cucumber	0.060
Radish	0.075
Young beans	0.089
Tomato	0.110
Lettuce	0.120
Potato	0.160
Celery	0.250

Salt-Poor Menu No. 1

	Food gm.	NaCl gm.	Protein gm.	Fat gm.	C. H. gm.
BREAKFAST.					
Orange	100	.005	1.0	—	10.0
Corn meal	30	.024	2.8	—	22.6
Bread (salt-free)	20	.014	2.0	0.2	11.0
Butter (salt-free)	10	.002	—	8.5	—
Liver, braised	80	.112	16.0	4.0	1.6
Lard	10	—	—	10.0	—
Honey	20	.010	0.1	—	16.2
Cream	50	.068	1.5	10.0	2.5
Sugar	40	—	—	—	40.0
Coffee or tea					
LUNCH.					
Cold pork	100	.100	25.0	14.0	—
Fresh lima beans	100	.015	7.0	—	22.0
Tomato	30	.028	0.3	—	1.2
Pork dripping	10	—	—	10.0	—
Lettuce	10	.012	0.1	—	0.3
Grapefruit	80	.006	—	—	4.0
Olive oil	20	—	—	20.0	—
Tapioca	20	.007	0.1	—	17.6
Cream	20	.028	0.6	4.0	1.0
Egg yolk	40	.016	6.4	13.4	—
Sugar	15	—	—	—	15.0
Sugar	20	—	—	—	20.0
DINNER					
Clear tomato soup	80	.075	0.8	—	3.2
Steak	90	.099	21.6	9.0	—
Lard	10	—	—	10.0	—
Boiled onions	10	.016	1.0	—	5.0
Bread (salt-free)	20	.014	2.0	0.2	11.0
Butter (salt-free)	20	.004	—	17.0	—
Lettuce	10	.012	0.1	—	0.3
Cabbage	30	.009	0.6	—	1.8
Gelatine	5	.036	4.2	—	—
Mayonnaise: Egg yolk	5	.002	1.1	1.7	—
Mayonnaise: Olive oil	30	—	—	30.0	—
Peaches	100	.006	1.0	—	9.0
Sugar	40	—	—	—	40.0
Cream	30	.041	0.9	6.0	1.5
Coffee or tea		—	—	—	—
Total		.761	96.2	168.0	256.8
Total calories	2924				

Salt-Poor Menu No. 2

	Food gm.	NaCl gm.	Protein gm.	Fat gm.	C. H. gm.
BREAKFAST.					
Grapefruit	100	.008	—	—	5.0
Oatmeal	20	.003	3.2	1.4	13.4
Cream	50	.068	1.5	10.0	2.5
Sugar	60	—	—	—	60.0
Bread (salt-free)	20	.014	2.0	0.2	11.0
Butter (salt-free)	15	.003	—	12.8	—
Scrambled egg: Water	10	.014	0.3	2.0	0.5
Cream	10	.014	0.3	2.0	2.5
Egg yolk	50	.020	8.0	16.5	—
Coffee or tea		—	—	—	—
LUNCH.					
Creamed salmon (fresh):					
Salmon	40	.024	8.8	4.8	—
Cream	30	.041	0.9	6.0	1.5
Butter	20	.004	—	17.0	—
Corn starch	5	—	—	—	4.5
Stewed rice	20	.008	1.6	0.1	15.8
Bread (salt-free)	20	.014	2.0	0.2	11.0
Butter (salt-free)	15	.003	—	12.8	—
Fruit salad:					
Lettuce	10				
Grapefruit or orange	100	.019	1.8	—	13.8
Apple	30				
Mayonnaise: Egg yolk	5	.002	1.1	1.7	—
Olive oil	30	—	—	30.0	—
Sugar	20	—	—	—	20.0
Fudge: Sugar	96	—	—	—	96.0
Butter (salt-free)	3	—	—	2.5	
Cocoa	5	.003	1.1	1.5	1.7
Water	10	—	—	—	—
Corn starch cookies:					
Cornstarch	45	—	—	—	40.9
Butter (salt-free)	25	.005	—	21.3	—
Orange juice	5	—	—	—	0.6
Sugar	8	—	—	—	8.0
DINNER.					
Roast Lamb	50	.045	10.0	6.5	—
Green peas	50	.029	2.0	—	8.5
Carrots	50	.010	0.5	—	2.5
Mint sauce: Water and vinegar					
Sugar	10	—	—	—	10.0
Mint					
Potato, mashed	60	.096	1.5	—	12.6
Butter (salt-free)	20	.004	—	17.0	—
Baked apple	120	.010	1.2	—	24.0
Hard sauce: Butter	10	.002	—	8.5	—
Sugar	30	—	—	—	30.0
Walnuts	5	.001	0.9	3.2	0.7
Sugar	20	—	—	—	20.0
Coffee or tea	—	—	—	—	—
Total		.450	48.4	176.0	414.5
Total calories	3436				

Salt-free bread and biscuits are raised with yeast, or sometimes beaten to lightness. No experiments have yet been performed to show whether soda or baking powders affect the blood pressure, but they are forbidden on suspicion. The taste of salt-free baked articles can be improved by sweetening slightly with sugar or mixing the dough with nuts, raisins, blueberries, etc.

Cornstarch Cookies

(Metric)	(Household measure)
480 gm. cornstarch.	1 lb. cornstarch.
90 gm. sugar.	3 tablespoonfuls sugar.
270 gm. butter (salt-free).	5/8 lb. butter (salt-free).
45 gm. orange juice.	3 tablespoonfuls orange juice.

Mix starch and sugar. Add butter, mixing thoroughly with the hands. Add orange juice. Roll and cut.

This quantity makes two dozen cookies.

Fudge

(Metric)	(Household measure)
960 gm. sugar.	2 cups sugar.
30 gm. butter (salt-free).	2 tablespoonfuls butter (salt-free).
50 gm. cocoa.	5 tablespoonfuls cocoa.
100 cc. water.	½ cup water.
Vanilla.	Vanilla.

The details of preparing appetizing diets by the use of condiments, of the widest possible variety though never excessive in quantity, would require a cook-book for their description; but a word is necessary here concerning some traditional prejudices as to foods or seasonings which must be avoided. These ideas have been carried along in text-books from a primitive period of medicine, and they rest on no proof that can be considered valid today. Good illustrations are furnished by von Noorden.[12]

This book of von Noorden is dated 1903, but was evidently written before the author became aware of the contemporary French discoveries of the relation of chlorides to edema or any other nephritic symptoms. Accordingly, it is stated (p. 77), that "Spices proper must be included among directly harmful and injurious articles, particularly irritating condiments like pepper, ginger, mustard, etc. Salt, vinegar and lemon juice on the other hand are not included in this class". To be avoided are (p. 78) white and black pepper, cayenne pepper, paprica, curry, cloves, vanilla (?), nutmeg, English and German mustard, anis, leek, garlic, caroway, knob celery and table celery, asparagus (?), mushrooms (?), morel and truffles. This prohibited list, together with horseradish, mint, thyme, sage, allspice, bay leaves, dill, caramel, coffee

and chocolate (as flavors), citron, orange and lemon peel, and the greatest possible variety of fruit and vegetable flavors give an idea of the means actually used for overcoming the flatness of the salt-free diet. In the absence of any accurate functional tests, general prudence would counsel the avoidance of any great quantities of these subtances which might conceivably irritate the kidneys; but there has been no indication of harm from the small amounts necessary for flavoring.

Von Noorden (p. 44) forbade cranberries, fruits containing kernels, and certain green vegetables on the purely imaginative ground that they contain benzoic acid, though there has never been any proof that the kidneys were ever injured thereby. Many physicians today still prohibit tomatoes from a similarly unfounded fear of acids. Von Noorden's ban upon radishes and celery was based upon observations of hematuria or increased albuminuria on isolated occasions when patients ate huge quantities of them. These are the very vegetables which are usually eaten with liberal additions of salt, and not only von Noorden's observations but perhaps also the only real basis of the fear of tomatoes may be thus explained. Vegetables of all kinds are a desirable feature of the diet, but when used in very large quantities their natural salts may exceed the renal function of a severe hypertension case. Under these conditions the total quantity of vegetables may be limited by substituting fruits, or considerable salt can be removed by boiling the vegetables and discarding the water.

12. *Remarks.* This column is devoted partly to complications and other special features, but chiefly to the ultimate outcome. Such results are sometimes difficult to summarize briefly; for example, there may occasionally be symptomatic improvement without appreciable lowering of blood pressure, and vice versa. Also, an initially favorable result may be spoiled if the patient breaks diet, or death from apoplexy or uremia may occur even though the blood pressure and all other symptoms were distinctly relieved and life apparently prolonged. The records of blood pressure and mortality may be allowed to speak for themselves. A further answer to questions concerning the benefit of salt restriction and the attendant reduction of blood pressure is contained in the fact that 121 of the 155 living patients have continued faithful to the treatment. Salt-free diets, though prepared so as to be tolerable, are irksome and above all are inconvenient, and such a high proportion of fidelity among a large series of patients scattered in various parts of the country is not possible unless the patients themselves are convinced of benefit.

PART II

Individual Features of Treatment and Illustrative Cases

Various practical and theoretical details will be discussed under the following headings. Though the opinions expressed must be based chiefly upon our general experience, a number of individual case histories are summarized, which will illustrate the type of observations upon which conclusions are based, and also incidentally make clear various features of the treatment.

1. *Results Not Due to Physical or Psychic Relaxation.*

Perhaps the simplest criticism likely to be made, especially when institutional treatment is described as an important aid to success in most cases, is that the therapeutic benefits observed are the result of institutional environment. Psychic stress, strain and worry, overwork, and overintensity in everything have been assigned such an over-important position among the imagined causes of hypertension, and physical rest has been so commonly employed as a palliative measure, that any relief obtained in an institution may be misinterpreted as due to physical, mental and emotional quiet. The following are a few case histories pertaining to this point.

Case No. 2105. Female. American. Age 55. Married. Housewife. Admitted July 22, 1922.

Complaint: Nervousness, irritability, insomnia, and occasional dyspnea on exertion.

Family history: No history of hypertension or any other metabolic disorders.

Past history: Has always been well, active and strong. Has had very few complaints and has suffered from no serious chronic or acute illnesses. Has always been free from headaches and has not suffered from shortness of breath, palpitation or edema. The diet has been normal and she has kept her body weight within normal limits. Has two children living and well. Her teeth gave considerable trouble until five years ago when all were extracted.

Present illness: Four years ago she became irritable and nervous and worried about herself and children without apparent cause. Has had insomnia intermittently, and when she had sufficient sleep noticed that she did not feel rested as formerly. Walking a short distance produced dyspnea and palpitation followed by fatigue and exhaustion. Had no headaches. Three years ago the pressure was found 210/110 by her physician, and it has ranged from 160 to 220 since. She has followed a low protein, meat-free diet carefully. Milk, cream, bread,

vegetables, fruit and butter have been the main articles of diet. Under medical advice she has avoided exercise, climbing stairs or walking any distance, and all possible mental or emotional stress. On four occasions she has spent long periods of time in institutions and health resorts for complete rest and relaxation. In spite of such treatment, pressures have remained elevated and her condition has not been improved. At the present time, insomnia and irritability are her chief causes for seeking treatment.

Physical examination: A well nourished and well preserved adult female, who appears to be about 40 or 45 years of age. Height 5 ft. 5 in., weight 132 pounds. She is slightly anemic, especially the sclerae and mucous membranes. Muscles are well developed and there is very little adipose tissue. The nose and throat are normal. The pupils react well to light and accommodation. Eye-grounds are free from choroidal or retinal changes. The arteries are very small but show no placques or hemorrhages. Maculae are normal. Lungs are normal. The heart shows no enlargement on deep or superficial percussion. No abnormal pulsation seen. Point of maximum impulse is in the MC line in the fifth interspace. Aortic second sound is accentuated and much louder than the pulmonic sound. No murmur heard at the apex. Pulse is regular. The radial arteries are thicker than normal and can be easily rolled under the fingers. There is very little tortuosity of any of the peripheral arteries. Blood pressure 224/110. Abdomen normal. Extremities normal. Reflexes present. Glandular and neuro-muscular systems normal.

Progress in the Institute: Salt-free diet, without limitation of protein, fat or carbohydrate was prescribed. She was required to take graduated exercises, beginning at first with short walks and climbing stairs slowly, but later walking several miles, which she did without complaint. Blood pressure reading showed gradual improvement on this program. Evening blood pressures taken after a day of such exercise were within the average ranges.

Salt-free diet was tolerated without inconvenience or symptoms of salt privation. Plasma chlorides fluctuated but tended to remain higher than the theoretical threshold of 563 mg. per 100 cc. Beginning August 2, 2 gm. of sodium chloride was added to the diet. There was immediate retention, as shown by the lagging of chloride excretion in the urine, since only about one-half gram was excreted in 24 hours. The plasma chlorides likewise showed retention to the extent of 628 mg. per 100 cc. on August 4. The blood pressures increased from the former level of 130 mm. systolic to approximately 175 mm. systolic. The patient was discharged August 5, and salt-free diet was prescribed on the basis of the information furnished by this test. The benefit has proved permanent.

Case No. 2105

DATE 1922	NaCl in Diet gm.	URINE				BLOOD			BLOOD PRESSURE	
		Vol. cc.	Spec. grav.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M
July										
18						123	606	22	224/110	
23										190/100
23	0	1240	1013	.618	4.26	123	552	38	222/111	208/105
24	0	1320	1012	.144	1.80				180/100	186/100
25	0	990	1015	.099	1.80	102	578	42	162/60	166/90
26	0	800	1011	.095					160/80	162/80
27	0	1270	1010	.045	.57					
28	0	580	1018	.062	.35				156/80	160/90
29	0	780	1012	.055	.42	127	593			
30	0	1190	1013	.051	.60				135/80	
31	0	500	1020	.055	.27				130/70	137/70
August										
1	0	780	1017	.053	.41				130/80	150/84
2	2	1150	1012	.045	.51				146/90	
3	2	960	1015	.074	.11				156/90	150/92
4	2	910	1013	.074	.67	115	628		180/90	178/88

Case B-472. Male. American. Age 47. Married. Physician. Seen February 13, 1922.

Complaint: Fatigue, irritability, precordial distress, excitability.

Family history: Mother died at 45 of Bright's disease. Father living and well at 67. No history of diabetes or other metabolic disease.

Past history: Always in good health. As a boy very strong, and while at college indulged heavily in athletic sports, on basket ball, baseball and football teams. Never suffered from headaches; no trouble with vision or need for glasses. Severe attack of tonsillitis four years ago. Five years ago the appendix was removed, on account of chronic appendicitis. Fever necessitated opening the wound for drainage of stitch infections. The peritoneal and deep structures were not involved. Drainage continued for about four days, and the temperature fell to normal. Pure culture of streptococcus was isolated. Used considerable tobacco, and for the past five years has noticed some palpitation of the heart when he smoked too much. Never had edema; appetite always good; never had gallstones or jaundice. Has never had nocturia or dysuria. Denies venereal disease. Wassermann test performed two years ago was found negative. Never obese. His body weight has been 172 lb. for the past ten years. Height 5 ft. 10 in .

Present illness: He has known of the existence of high blood pressure for the past four years. The first examination, made more or less by accident, showed 165/88. He thought the pressure temporary, and attributed it to tobacco. He stopped smoking for several months, but no decrease resulted. During the first year the pressure ranged from

145 to 165 mm. systolic, 70 to 90 diastolic. He has been very active as a physician, and has had to make numerous night calls.

During the past two years blood pressures have been taken on an average of 2 to 5 times a week, under varying conditions. On the whole, they have steadily increased, and recent readings have been as high as 220 systolic and 130 diastolic. Smoking has had little influence on the pressure. He smokes one to three cigars a day, and notices a little rise, which he attributes to it. During the past two years he has suffered considerably from palpitation and a feeling of fullness and oppression over the precordium, especially during excitement. After a hard day's work or long hours of night duty the oppression has been sufficient to produce insomnia. He has had no anginal attacks, neither has he suffered from headaches or blurred vision. No evidence of edema. Small granular casts have been present the greater part of the time during the past three years, but he has at no time found albumin.

During the first year of the disease he ate but little protein, his meals consisting for the greater part of vegetables, cereals and milk. No effect was noted in the pressure. He has refrained from using drugs of any kind, and on the whole has felt well and been able to carry on the duties of an active practice. He has realized the seriousness of his case, but has tried to worry about it as little as possible.

Physical examination: Muscular, well developed, adult male. Hair is thick and bushy, with a few grey hairs over the temple region. Temple vessels are thickened and slightly tortuous. Eyes: pupils are equal, and react normally to light and accommodation. Eye-grounds show discs to be well formed and the outlines clear and distinct. Arteries are smaller than normal. Macula normal. Thyroid palpable, but not enlarged. Chest large with deep anteroposterior diameter. Percussion note is resonant over the whole chest area. Heart: P. M. I. is in the MC line in the 5th interspace. Superficial and deep cardiac dullness is increased on percussion. No shocks or thrills; no precordial bulging or heaving. Aortic second sound loud and accentuated. No murmur at the apex. The radial and brachial arteries are thick but not especially tortuous. Blood pressure 222/130, taken after patient had been quiet for about thirty minutes. Height 5 ft. 10 in. Weight 190 lb.

Laboratory: Blood urea 36, plasma chloride 591, plasma sugar 127 mg. per 100 cc. Urine: 24 hour volume 1400 cc.; specific gravity 1016; pale straw color; no albumin or casts; chlorides 0.58 per cent; total NaCl 8.12 gm.

Progress: This patient was treated at his home on account of the fact that he could not spare time from his practice. He carefully avoided salt without changing the protein or the total quantity of food. Blood pressure readings were made twice daily. Gradual improvement was noted during eight days, when the pressure reached 140/90. On account of the salt restriction, he experienced some weakness and lassitude, as compared with his former feeling of tenseness and nerv-

ousness. Specimens analyzed for chloride have ranged from 0.4 to 0.8 gm. in 24 hours.

The systolic pressure has remained below 160 mm., notwithstanding continuance of heavy professional work during the entire treatment. Various 24-hour urine specimens have contained 0.4 to 0.8 gm. of sodium chloride. The margin of tolerance is narrow, for with the strictest salt privation there is some tendency to weakness and lassitude, and increases of salt above 1 gm. bring on rise of pressure and nervousness.

No. 522. Female. American. Age 50. Married. Housewife. Admitted April 15, 1921.

Complaint: Occipital headaches, nervousness, irritability, and palpitation of heart.

Family history: Mother died at 60 of heart trouble. Father died at 70 of pneumonia. One brother and one sister have tuberculosis.

Past history: Had the usual childhood diseases. Was always in fairly good health, with the exception of chronic gastritis between the ages of 21 and 30. Several Wassermann tests performed during the past six years have been entirely negative. Patient married 14 years; has had 3 miscarriages. In 1909 had eclampsia, and abortion was performed. She had numerous convulsions with unconsciousness. At that time the blood pressure was found elevated, and albumin and casts were present in the urine.

Present illness: Since 1910 she has suffered from occipital headaches, which come on early in the morning but often persist until late at night and keep her awake. She has had albumin in the urine constantly since 1913, during which time she has suffered from shortness of breath, especially on exertion, and a clutching sensation in the throat. In April, 1915, she had sudden aphasia; was clear mentally but was unable to call the names of objects and her speech was indistinct. She clearly recognized her friends but was unable to call them by name. An hour later she had twitching of the muscles of the right side of the body, followed immediately by complete paralysis. The paralysis was of a temporary nature and cleared entirely after about two weeks. In October, 1915, she had a sudden stroke, accompanied by unconsciousness and convulsions. The blood pressure was found 250/140. She recovered slightly from the stroke at first, but has never regained sufficient control of the arm to use it for writing or sewing. She has felt well with the exception of nervousness, irritability and dyspnea. For the past five years she has been on a closely restricted protein diet and has used principally cereals, vegetables, fruits, butter, bread and cream. Blood pressures have ranged from 180 to 240 mm. systolic. At no time has she had edema. She has led a life of practical invalidism, the family insisting that she perform no work and that she remain in bed or quietly about the house the greater part of the time. She has been to numerous health resorts in the past five years in order to obtain relaxation. She has gained 30 pounds in weight in the past four years.

Physical examination: Well nourished adult female. Height 5 ft., 4 in.

Weight 136 pounds. The skin is clear. The face is flushed and there are a few very fine dilated venules over the cheeks. She walks with hemiplegic gait. There is paralysis of the right arm and leg. The hand remains partially adducted. She is unable to grasp small objects or to hold firmly other objects when placed in the palm. The grip of the right hand is very weak. She has slight residual accommodation. Eye-grounds show definite sclerosis. The terminal endings of some of the arteries are very small and threadlike. There is no choroiditis. Heart is enlarged 2 cm. to the left. On percussion, the left border of the heart is 17 cm. from the mid-sternal line. Increased dullness over the manubrium. Well marked pulsation can be felt in the sternal notch. There is no murmur at the apex. Aortic second sound is accentuated. Blood pressure 226/118. Liver is palpable but not tender. Reflexes of the right arm and leg are increased. Urine shows faint trace of albumin with a few hyalin casts.

Progress in the Institute: Treatment consisted of rigid salt-free diet

Case No. 522

DATE 1921	NaCl in Diet gm.	URINE				BLOOD			BLOOD PRESSURE	
		Vol. cc.	Spec. grav.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M
April										
15	0	625	1010	.486	3.037				226/118	
16	0	1400	1010	.165	2.310				210/120	
17	0	750	1008	.293	2.197					222/117
18	0	1370	1008	.152	.562					222/117
19	0	1020	1008	.041	.418				195/105	
20	0	1000	1008	.042	.420				195/105	
21	0	1050	1010	.045	.472					205/115
22	0	1030	1010	.045	.463				200/100	170/90
23	0	790	1010	.041	.323					170/90
24	0								182/95	
25	0	1000	1010	.041	.410					
26	0	780	1010	.045	.351				160/88	
27	0	1200	1010	.020	.240				160/88	
28	0	1100	1010	.024	.264				160/88	
29	0	1225	1012	.120	1.470					170/110
30	0	1000	1012	.152	1.520					170/90
May										
1	0									
2	0	950	1012	.165	1.567					183/100
3	0	670								177/90
4	0	1000	1013	.086	.860					
5	0	640	1013	.060	.384					
6	0	1350	1012	.044	.594				152/84	
7	0	530	1010	.086	.455					
8	0	1075	1010	.004	.043					170/85
9	0	1000	1012	.044	.040					
10	0	1015	1010	.044	.446					
11	0	625	1012	.012	.075					172/100
12	0	1210	1008	.012	.145	108	583	30	168/97	

with unlimited protein, fat and carbohydrate. She was persuaded to eat meat and eggs in normal quantities. She was encouraged to take considerable outdoor exercise each day, instead of the complete rest and avoidance of exertion which had been her former rule. The exercise was graduated so that upon discharge she walked 2 miles or more about the grounds and was able to climb moderate slopes. The blood pressure gradually fell as shown in the table, and the general strength increased. Dyspnea, although present on exertion, improved markedly during her stay. She complained of palpitation on onty a few occasions. Fixation of the urinary concentration is indicated by the fairly constant specific gravity, never above 1013. The urinary chloride fell below 0.5 gm. within 4 days. The elevated output, April 29 to May 2, apparently represents the emptying of some chloride store, and the blood pressure then fell further. The patient was discharged May 12, 1921, and advised to take a normal diet, with the exception of salt, and to exercise as she desired.

Physical rest has not been a feature of the treatment. No patient has been put to bed, unless for a critical emergency acutely threatening life at the time of admission, and patients arriving in this state have with favorable progress been allowed to be up and about within a few days. Patients who had not walked up a flight of stairs for years, because of either physical inability or medical prohibition, have been assigned to upper rooms without an elevator and have been allowed not only to traverse two flights of stairs several times daily, but have also been encouraged to walk considerable distances in and outside of the grounds. No harm has resulted in any instance. The general health is undoubtedly improved, and the sense of invalidism diminished. The evening blood pressures are by no means always higher than those of the morning; but even if there is a slight transitory rise of pressure, we suspect that the general improvement of circulation and muscular vigor contributes slightly toward ultimate improvement of the blood pressures. The basis of the improvement permitting such activities is believed to be the salt-free diet. We have tried rest cures for cases of the more difficult type, but in no instance have the blood pressure and attendant symptoms, which have proved refractory to diet, been appreciably relieved by bed rest. The relief by physical and mental rest, which is undoubtedly obtainable in less severe cases, is temporary, in contrast to the lasting effect of the diet treatment. Satisfactory results have been obtained with home treatment, when the conditions permitted exact dieting, while the patient

carried the full burden of his business affairs. After successful institutional treatment, patients have been enabled to resume heavy responsibilities without return of symptoms. Relapses have occurred when the diets have been violated at home, and have been terminated by exclusion of salt without other change in the habit of living (cf. cases No. 656, p. 514, No. 63, p. 521, No. 971, p. 479, and No. 429, p. 502. For these reasons, we believe that physical or psychic relaxation is not an essential factor in our results.

The fact that the diet treatment generally enables patients to undertake increased physical and mental activity does not conflict with the recognized fact that overstrain temporarily raises blood pressure, and that damaged blood vessels should not be subjected to unnecessary tension. The recovery of power to endure moderate exertion is important, but the advice given concerning the mode of living still emphasizes moderation in work and exercise and the avoidance of all excesses.

A comparison naturally suggests itself with the similarly exaggerated importance which has been attributed to nervous influences in diabetes. There is no doubt that excitement and emotion can raise the blood sugar of diabetics higher than that of normal persons, and in uncontrolled cases may sometimes increase the sugar excretion in the urine. In a large series of cases, however, under thorough dietary control we have never seen a single instance of glycosuria or alteration of assimilative power from mere emotional causes. Nervous strain is recognized as detrimental and to be avoided if possible, but it is not a fundamental element in either diabetes or hypertension.

2. *Results Not Due to Reduction of Protein.*

In addition to the cases just described, the following examples may be given.

Case 1164. Male. American. Age 51. Married. Auctioneer. Admitted June 18, 1922.

Complaint: Headaches.

Family history: There was a marked family history of nephritis and cardiac disease. His father died at 74 of apoplexy, and his mother at 49 of Bright's disease. A maternal uncle and aunt died of apoplexy.

Past history: His general health was good. With the exception of typhoid fever at 17, he had no serious illnesses. One of his greatest troubles was overeating; he enjoyed good food and ate carbohydrate and fat to excess for many years. His work during certain seasons of the year required long, arduous hours, and he was accustomed to use

alcohol to excess when he became fatigued. For many years he has taken unusual quantities of salt in the diet, often finishing a meal by eating pure salt. His average weight was about 180 pounds, but he had noticed a gradual decline the past two years. He never suffered from dyspnea, palpitation, cardiac pain or edema.

Present illness: One year ago severe headaches developed intermittently and increased gradually in intensity. They usually began in the morning and would grow worse during the day. On over-exertion, especially on days when his work as an auctioneer called for unsual mental and physical activity, the pain was severest. Following a day of such work it would be necessary for him to rest several days. His blood pressure a year ago was found high. His physician prescribed a carbohydrate and fat diet, without meats of any kind, except chicken occasionally. He followed this advice strictly, and continued to use large quantities of salt as before.

Ten days ago an attack of headache occurred rather suddenly with intense pain over the frontal and occipital regions, at times being sufficiently severe to require morphine. He also complained of pressure sensation over the frontal region. It became necessary to remain in bed and be as quiet as possible. Nevertheless, the headaches grew worse rather than better.

Physical examination: Moderately obese adult male. He is somewhat dull and stuporous, is in great distress and pain on account of severe headaches, and keeps his hand pressed against his forehead the greater part of the time. He walks slowly with guarded gait, complaining that jarring and noise intensify his pain. The eyes react normally to light and accommodation: pupils of equal size; normal fundi and normal maculae. Lungs are normal. The heart is only slightly enlarged to the left, P. M. I. being about ½ cm. outside MC line in 5th intercostal space. Blood pressure 240/150. Aortic second sound accentuated; no murmurs at apex. Slight increase in area of superficial and deep cardiac dullness. Slight thickening of temporal, radial and brachial arteries. Liver and spleen normal. Height 5 ft., 7½ in.

Progress in Institute: Treatment in the Institute was of two weeks' duration. The laboratory findings are shown in the table. The diet was unrestricted in protein and calories but was as strictly salt-free as possible. On the second day the patient noticed gradual remission of headaches, and on the fourth day was entirely comfortable. At first he found the salt-free diet monotonous and unpalatable, but he became accustomed to it within a few days. Blood pressure readings made twice daily showed slow and gradual improvement, but there was a marked tendency for the diastolic pressure to remain fixed at about 120 mm. The urine regularly contained traces of albumin. He was discharged on July 2, 1922, with instructions for strict salt-free diet.

Progress after discharge: The patient has followed diet with scrupulous care. He has made eight office calls at regular intervals since discharge. Twenty-four hour urine specimens were analyzed on each occasion, but at no time has the total chloride excretion exceeded one gram, with urine volumes ranging from 900 to 1300 cc. There has

been slow, gradual decrease in blood pressure at each office call, the maximum being 147/87 and the minimum 128/78, with a general average of 136/83. He has had no return of headache or symptoms of hypertension, such as dyspnea, irritability, fatigue or palpitation. Physical examination performed on December 23, 1922, showed the heart to be normal in size, the P. M. I. being in the MC line in the fifth interspace. Blood pressure was 128/78, and heart sounds normal. Urine specimen examined January 15, 1923, was negative for albumin.

Case No. 1164

DATE 1922	NaCl in Diet gm.	URINE				BLOOD			BLOOD PRESSURE	
		Vol. cc.	Spec. grav.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.
June										
18	0	650	1022	.934	6.07	143	606	24		230/150
19	0	600	1022	.672	4.03	143	606	24		180/118
20	0	600	1022	.500	3.00				174/110	202/110
21	0	650	1024	.144	9.36				170/120	174/100
22	0	810	1023	.084	.68					160/96
23	0	790	1023	.078	.62				172/110	170/110
24	0	790	1023	.177	1.39	143	573		184/110	170/100
25	0	715	1022	.075	.536				150/90	170/116
26	0	870	1024	.066	.574	170		60	170/110	180/130
27	0	700	1025	.153	1.071				180/130	180/110
28	0	730	1023	.107	0.787	113	570	19	160/100	
29	0	725	1023	.086	.523				160/100	170/120
30	0	680	1025	.066	0.448				166/120	170/120
July										
1	0	615	1023	.070	0.430	150	573	50	170/120	

Case No. 974. Female. American. Age 57. Married. Housewife. Admitted January 11, 1922.

Complaint: Nervousness, irritability and obesity.

Family history: Mother died at 71 of heart trouble; she was always thin. Father died at 63 of angina pectoris; was not overweight. Three brothers, living and well, have no diabetes, nephritis or hypertension. Patient married 25 years; one son killed in accident at age of 25.

Past history: General health was always good. She had measles, mumps, and whooping cough as a child. Never had typhoid or influenza. Two years ago she had rheumatism in the feet, with swelling and tenderness of the ankles and knees, associated with considerable pain. An X-ray examination showed "deposits" about the joints of the knee. She has had no dizziness or headaches. She suffers frequently from sinus trouble and colds, but never had tonsillitis. Two months after the onset of rheumatism, an impacted and infected tooth was removed. In

1910 she noticed thyroid gradually increasing in size. Diagnosis of toxic goitre was made. She had the classical symptoms of palpitation, tremor, irritability and shortness of breath. Partial thyroidectomy was performed in 1911 and again in 1915, with improvement in her general health, and tonsillectomy in 1919. She has not suffered from abdominal cramps or pain, gallstone attacks or jaundice. For 12 years she has had nycturia and polyuria. Extrauterine pregnancy in 1894 was operated upon, and the recovery was uneventful.

She was always inclined to obesity. As a young woman she was very stout and there were always large deposits of fat about the thighs and chest. She has often reduced her weight by close dietary restriction, but gained rapidly on increased diet.

Present illness: She has known of the existence of high blood pressure for seven years. For the past six years shortness of breath has been extreme at times, accompanied by attacks of dizziness and a feeling of fullness in the head. She has suffered from hot flushes, especially of the face and neck, for the past two years. Her chief complaint is fatigue and prostration, which come on without apparent cause. After a night's sleep she does not feel rested. There has been a complete lack of ambition which she is unable to explain. There has also been nocturnal polyuria from 10 P. M. to 7 A. M., the volume often exceeding 1300 cc., with specific gravity from 1012 to 1016. During the past four years she has followed a diet of closely restricted protein, avoiding meat and eggs altogether. Her weight has ranged from 190 to 205 pounds, and she found it difficult to reduce. Recently she has tried omitting salt, without benefit. Laboratory tests performed November 15, 1921, were as follows: Urine: trace of albumin and a few hyalin casts, specific gravity 1013, sugar and acetone negative, phenolsulphonephthalein test 55% in 2 hours. Blood: urea 34 mg., sugar 80 mg. per 100 cc.; Wassermann negative.

Physical examination: A plethoric obese woman of nervous appearance. Height 5 ft. 3 in.; weight 190 pounds. Lips and fingers cyanotic. She is very highly complexioned, face often suffused crimson. Eyes react slowly to light and accommodation. Eye-grounds normal. Teeth in good condition. Tonsils have been removed. There is no general glandular enlargement. Percussion note over the chest is resonant in both front and back. No rales at the bases. The heart shows moderate hypertrophy, the left border extending 1 cm. to the left of MC line. Increased retromanubrial dullness. There are no shocks or thrills. Aortic second sound accentuated. There is a systolic murmur at the apex which is poorly transmitted. Blood pressure 224/124. Pulse 80 per minute, regular. Abdomen normal. Reflexes normal. No edema.

Progress in the Institute: Following her admission on January 11, 1922, salt was excluded as usual, and she was given chiefly protein and carbohydrate, fat being restricted to reduce weight. 6.77 gm. of chloride was excreted the first day, in spite of the fact that she had been advised by her physician to take a salt-free diet at home. She had not added extra salt to her food, but it had been used in cooking.

As shown in the table, the chloride excretion rapidly fell to 0.74 gm. on January 15. At that time she began to show indications of salt privation, namely, weakness and fatigue. On January 17, on arising in the morning, she felt dizzy and weak. She had pain in the calves of the legs, and on attempting to walk could scarcely do so on account of lassitude and weakness. She had entirely lost appetite and food was repulsive. She complained of nausea, but there was no tendency to vomit. Weakness gradually increased throughout the day. Salt was not added to the diet, but instead, she was given substitutes such as lemon juice, vinegar, horseradish and salt-free mustard. Examination showed the pulse to be 64 to 70 per minute, as compared to her former pulse rate of 80 per minute. She was listless, moved slowly and her speech was markedly less rapid than usual. Her complexion was pale, as compared to her former brilliant color. Plasma chloride analysis during the attack was 568 mg. per 100 cc., as compared with 610 mg. per 100 cc. on the first examination. Depression and weakness persisted until 2 gm. salt was added to the diet on January 26. This addition

Case No. 974

DATE	NaCl in Diet gm.	URINE			BLOOD			Blood Pressure		Body Weight lb.
		Volume cc.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.	
1921										
Dec. 9					132	610		224/124		
1922										
Jan.										
11	0	1100	.618	6.77	139	573		188/130	180/120	190
12	0	900	.470	4.23	139	573		190/130	180/110	
13	0									
14	0	1500	.091	.615				180/120	180/110	186
15	0	1400	.053	.74				190/120	180/100	
16	0							168/104	180/100	
17	0	1400	.045	.63	143	568	26	160/100	170/120	
18	0	1900	.033	.62					170/100	188
19	0	1200	.016	.19				140/100	152/90	
20	0	1550	.024	.37				150/100	152/90	
21	0	1250	.041	.51	152	597		160/110	160/108	185
22	0	1900	.040	.77			26		158/96	
23	0	1550	.041	.75						
24	0							160/90	162/100	185
25	0	1450	.012	.17				165/100	140/100	
26	2	1100	.033	.36	135	544	22	148/82	160/96	
27	2	1700	.041	.69				140/90	140/90	186
28	2	1300	.115	1.49				158/96	152/90	
29	2	1300	.140	1.82				150/120	158/100	
30	2	3300	.140	4.62				150/120	150/100	
31	2	1800	.091	1.63	143	552	22	150/100	150/100	183

gave prompt and complete relief. During her stay in the hospital there was gradual remission in the blood pressure readings, as shown in the table, and she felt entirely well.

Progress since discharge: Following her discharge on Janury 31, she remained at home on a diet containing 2 gm. salt until July. During that time numerous blood pressure readings were made by her family physician, who reported them to average 150/90. Analysis of the 24-hour specimens revealed outputs of from 0.7 to 2.9 gm. of sodium chloride. In July she went to the country where she was unable to obtain an accurate diet. Symptoms of irritability, nervousness and dyspnea returned in spite of the fact that she was less active than she had been at home. She came home in August and resumed accurate diet, and blood pressure readings have remained low. Urine examinations since December 1, 1922, have failed to reveal albumin or casts.

Case No. 457. Female. American. Age 56. Married. Housewife. Admitted February 6, 1921. Re-admitted January 23, 1922.

Complaints:. Weakness, nocturia, loss of weight, dyspnea, flushes, "paralysis".

Family history: Negative.

Past history: Healthy life, until 20 years ago, while in the fifth month of pregnancy, she became edematous and nauseated. Abortion was performed immediately and the symptoms rapidly disappeared. Spontaneous menopause occurred at 35. Three years ago bilateral oophorectomy was performed on account of cysts.

Eight years ago, extraction of three ulcerated teeth resulted in osteomyelitis of left inferior mandible and required five months of hospital treatment. Two months later diabetes appeared suddenly with classical symptoms. Glycosuria was controlled by diet for three months but has since been continuous. During these eight years the weight has fallen from 147 lb. to the present 117 lb.

She has suffered from indefinite dull headaches nearly all her life. Five years ago the right antrum was drained of a large quantity of pus, and healed after two months.

Present illness: Hypertension was first noticed 4 years ago. The first symptoms were transitory dizziness and slight morning headaches. These increased within a year and palpitation, precordial pain, and nose-bleeds became added. August 20, 1920, she awoke at 4 A. M. unable to lift her left arm. On attempting to walk she fell to the floor because of inability to use her left leg. She was immediately put to bed and a physician found her pressure 220/130. Power of speech was absent for one week. Dysphagia was troublesome and has continued to some extent to the present. Two days after the acute onset diplopia with blurred vision occurred and persisted for two weeks, gradually disappearing entirely after a month. Complete function of the left leg was slowly regained and at present there are no symptoms or complaints of a residual paralysis. The left arm was slower in recovering, but is now practically restored in usefulness except for some movements of precision with the thumb and index

finger. She has suffered increasingly with dizziness, weakness, nervousness, irritability, excitability, oppression, cardiac palpitation and pain, headaches, feelings of fullness in the occipit, and nocturia to the extent of eight or ten times per night. The systolic blood pressure during the past four years has ranged continuously between 200 and 230 mm. Albuminuria has been absent but casts constantly present. All meats have been avoided, and the diet has therefore contained considerable carbohydrate, in spite of the diabetes. Rest has been enforced to such a degree that the patient's life has been practically that of an invalid.

Physical examination: Height 5 ft. 2¼ in. Weight 117 lb. Fairly well nourished adult female, appearing slightly anemic, though with flushed cheeks and lips slightly cyanotic. Slight exertion causes complaints of breathlessness. There is a slight residual paralysis of the right side of the face, with drooping of the eye-brow and lip and partial loss of control of the Corrugator supercilii. The tongue protrudes to the left without quivering. Eyes: pupils equal and regular; reaction to light normal; eye grounds pale, with small tortuous arteries and enlargements of veins where they are crossed by the arteries; several small whitish placques along the arteries; maculae normal. The heart is enlarged to the left. There is slight heaving with each systole. Sounds clear. Pulse 75, regular. Blood pressure 230/110. Radial and brachial arteries palpable. Liver edge palpable but without pain or tenderness. Normal reflexes are present in the left arm and leg. The arm is somewhat weak, but touch and stereognosis are unimpaired.

Progress in the Institute: As shown in the table, the patient was placed on a salt-free diet of 40 gm. protein and 5 gm. carbohydrate. The diabetes proved to be mild, and it was soon possible to raise the protein allowance to 70 gm. daily. The patient had to be persuaded that it was safe for her to take such quantities of meat. It is noticeable that the blood pressure was not influenced adversely as the protein was increased. The strength gradually improved and all the other symptoms diminished. The patient was advised to remain outdoors almost the entire day, and to climb one flight of stairs per day. At discharge on April 1, 1921, the blood pressure was 169/70. At her home in Wisconsin she was able to do her own light housework, and her urine samples sent for analysis never contained more than 1 gm. of sodium chloride in 24 hours. During a pleasure visit to the East she entered the Institute in January, 1922, purely for observation purposes. Her blood pressure was then 165/70, and during her week's stay was never above 167/75. She had also remained free from glycosuria or any marked hyperglycemia.

As the treatment of hypertension by protein restriction is as widespread as it is unwarranted in ordinary cases, we have intentionally defied this tradition by giving diets liberal in protein and particularly in red meat in all cases without significant nitrogen retention. Contrary, therefore, to the

Case No. 457

DATE 1921	DIET			Plasma NaCl mg. per 100 cc.	Plasma Sugar mg. per 100 cc.	Blood Urea mg. per 100 cc.	Blood Pressure		Body Weight lb.
	Protein gm.	C. H. gm.	Total Calories				A. M.	P. M.	
Feb. 6	40	1	89						117
" 7	40	5	317		223	22			
" 8	40	5	364				230/110	200/100	
" 9	40	5	345	621	151	22	175/100	200/108	
" 10	40	5	422						
" 11	40	5	339						
" 12	50	3		601	152		188/80		
" 13	50	3	400						
" 14	50	3	400						115
" 15	50	3	400		140				
" 16	50	3	400						
" 17	50	3	500		136		198/75	152/68	
" 18	50	3	500				196/85		
" 19	50	3	500					168/75	
" 20	30	3	354		156		195/110	182/110	
" 21	50	3	500				197/77		
" 22	50	3	500		195			204/90	
" 23	50	3	500						
" 24	50	3	500						
" 25	50	3	500	610	138		192/78		
" 26	60	5	800				178/72		
" 27	60	5	800					182/70	114
" 28	60	5	800		161			180/80	
Mar. 1	60	5	800				174/74	184/82	
" 2	60	5	800					174/70	
" 3	60	5	800				172/76	164/66	
" 4	60	5	800				177/81		
" 5	60	5	800		142		177/86	153/70	
" 6	65	5	1000						110
" 7	65	5	1000				167/70		
" 8	65	5	1000					182/102	
" 9	65	5	1000		168			156/180	
" 10	65	5	1000		168		158/71	175/90	
" 11	65	5	1000		161				
" 12	65	5	1000		161		182/80		110
" 13	65	5	1000				175/82	175/82	
" 14	65	5	1000						
" 15					130				
" 16									108
" 17	65	8	1192		164				
" 18									
" 19	65	8	1192						
" 20	65	8	1192						
" 21	65	8	1192		187				
" 22									
" 23	65	8	1192						108
" 24	65	8	1192						
" 25	65	8	1192						
" 26	65	8	1192		110				
" 27	65	8	1192						
" 28	65	10	1800						
" 29	65	10	1400	568	125				
" 30	70	15	1400						108
" 31	70	15	1400						
Apr. 1	70	15	1400				169/70		

supposition that salt-free diets connote protein limitation because meat is eaten in less amount when unsalted, this treatment has often represented a sudden multiplication of the quantity of meat or protein formerly taken, causing joy to some patients and temporary apprehension to others. The reduction of blood pressure has not been impeded by this protein ration in average cases, and trials of extreme protein restriction have not improved the results obtained by the sole restriction of chlorides in refractory cases. Protein limitation has been used in the group of nephritic cases with a tendency to nitrogen retention, and the results have not been better in this than in the other groups.

The arteriosclerosis produced by earlier investigators in rabbits with carnivorous diets was due to cholesterol, but Newburgh[75, 76] has recently obtained arteriosclerosis due strictly to protein feeding. As such a multitude of agencies are known to give rise to vascular lesions in this species, these interesting experiments furnish no more proof that human arteriosclerosis is caused by protein than that it is caused by cholesterol. The results that may be obtained in omnivorous species will carry greater weight, but any injuries resulting from either putrefactive or normal digestive products on a diet restricted unnaturally to protein alone will still not prove that a normal proportion of protein in the human diet is injurious.

The experimental sclerosis, affecting preeminently the largest arteries, has not been shown to be accompanied by hypertension. The Eskimos on their extraordinarily protein-rich diet, according to the unique Krogh[77] report, are not noticeably subject to renal or vascular disease.

In the present treatment, it has not been considered prudent to place an abnormal burden of nitrogen excretion upon kidneys presumably damaged in their blood supply and possibly in their epithelium. It is conceivable that such a burden might tend to impair not only the nitrogen excreting function but also indirectly the function of salt excretion. Therefore eighty to one hundred grams per day has been considered a liberal allowance for such patients, and no trials have been made of excesses running into hundreds of grams daily. The clinical tradition is that these patients are susceptible to injury from such ordinary quantities of protein foods, and the

question can scarcely be settled except by direct clinical tests. To our minds the question is answered by the negative immediate influence of protein upon blood pressure in cases with or without nitrogen retention, the easy reduction of hypertension by salt restriction even when accompanied by a large increase of protein intake, and the absence of signs of delayed or progressive injury in observations extending up to three years.

3. *Results Not Due to Undernutrition.*

It will suffice to give one of the many case histories which establish this point.

Case No. 2041. Male. American. Age 60. Married. Real estate broker. Admitted April 1, 1922.

Complaint: Headaches, palpitation, dyspnea on exertion.

Family history: Tuberculosis has been prevalent, but no hypertension, arteriosclerosis or apoplexy.

Past history: Had measles, mumps, chicken-pox, and whooping cough as a child. As a young man was always under weight; at 21 years of age he weighed only 121 lb. with a height of 6 feet. Shortly after, tuberculosis was diagnosed. He then gained weight to about 211 lb. at the age of 37 years. He lived an outdoor life, but drank considerable alcohol, between the ages of 22 and 37; after 37 he stopped drinking. At the age of 43 he intentionally reduced weight, and developed pneumonia with pleurisy. On two other occasions when he attempted to reduce his weight he also developed pleurisy, which on one occasion was of a serious nature. For the past twenty-five years he has suffered from indigestion and pains after eating, also from hyperacidity, which was relieved by a bland diet. Several X-ray series showed no organic changes. He has always been nervous, overactive and a hard worker. Syphilis is denied, and two Wassermann tests were found negative.

Present illness: His present trouble began about 1912, after an attack of pneumonia. His chief complaint was severe frontal headaches, which came on irregularly and lasted from six to forty-eight hours. On many occasions he was incapacitated for work on account of the pain. For several years he used coal tar products for them, but relief was not always obtained. During the past year he has been accustomed to take from 1 to 1½ grains of caffein, or 1 to 1½ cups of coffee, since he found them effective in relieving headache. Excitement does not cause headache, but may increase it. High blood pressure has been known to exist for about eight years. At first the systolic pressure was 170 mm., then slowly increased, and recently has been as high as 222. He has tried all kinds of treatment—iodides, starvation, meat-free diet, and on one occasion reduced his weight from 174 lb. to 150 lb. without effecting a reduction in pressure. He suffered occasionally from palpitation and dyspnea on exertion. He has noticed

that during such attacks his lips become purple. On account of cardiac palpitation he found it necessary to give up golf, which he had been accustomed to enjoy for a number of years. For the past two months he disregarded diet and gave up treatment entirely.

Physical examination: Fairly well developed adult male of large osseous frame. Slightly dyspneic after climbing stairs. He is high complexioned, and there are numerous venules over cheeks and nose. Lips are slightly cyanotic. Head: complains of severe frontal headaches. Eyes: slight arcus senilis; pupils small, of equal size, react to light and accommodation. Eye-grounds are negative except that the arteries are smaller than normal. No choroidal changes. Lungs negative; no rales. Heart: enlarged 2 cm. to the left. Apex beat is 1 cm. outside MC line, and a systolic mumur is present at the apex. Aortic second sound is accentuated. Radial and brachial vessels are thickened. Blood pressure 218/112.

Progress in the Institute: Preliminary blood specimen showed urea 28, plasma chloride 626, plasma sugar 156 mg. per 100 cc. Urine contained faint trace of albumin but no casts. A salt-free diet, liberal in protein, fat and carbohydrate, was prescribed. The chloride output in the urine during the first 24 hours was more than 8 gm. Previous to admission, he had attempted to carry out a salt-free diet at home, without success. During his stay in the Institute there was a gradual decrease in the daily chloride output to less than 1 gm. Urine volume averaged about 1000 cc. daily. There was a gradual decline in the plasma chloride, from 626 mg. on admission to 523 mg. on discharge on April 8. Blood pressure readings were made morning and evening, and a steady improvement was noted. On the third day after admission the headaches ceased entirely and have not returned up to the present time. He discontinued taking coffee between meals at this time. Symptoms of salt privation, namely, listlessness, slight depression, fatigue, and dull pain in the calves of the legs were experienced on the sixth day, but subsided several days later without addition of salt to the diet.

Progress after discharge: A return office call was made on April 17, 1922. Blood pressure taken immediately after walking into the office was found 196/100, and the second reading made 20 minutes later was 182/90. He experienced some difficulty in obtaining a proper diet at home. A 24-hour urine specimen which he submitted showed 0.345 per cent NaCl in a volume of 900 cc. Headaches did not occur since his discharge. He had experienced no return of symptoms of salt privation. Blood findings were: urea 20, chloride 597, sugar 120 mg. per 100 cc. May 15, 1922, a second office call was made, when he had distinct symptoms and signs of salt privation. He walked slowly, and his speech was calm and quiet, as compared with rapid movements and quick speech on former occasions. He complained of becoming easily fatigued, and preferred to remain quiet rather than to exert himself to any extent. He insisted on carrying out the same rigid program, since the headaches had not returned. The blood pressure reading was 163/95 immediately after walking into the office. The 24-hour

urine specimen contained only 0.7 gm. of sodium chloride. He made another office call on June 2, and again on June 19, when blood pressure readings were found 176/110 and 168/90. During the summer he again took up golf, which he played daily without a return of the headaches or palpitation.

Reduction of weight, as mentioned, had never benefited this patient, and on the other hand the benefit described was accomplished without any reduction of weight.

The alleged rôle of undernutrition was largely settled by the observations in Part I, namely, that it is effective only in the milder cases, especially those in which obesity is a slightly aggravating influence, and in the majority of our patients the body mass has not been reduced; furthermore, the continuance of the treatment for periods up to several years with retained weight and strength excludes any chronic undernutrition. In our experience undernutrition within feasible limits has shown no appreciable influence in reducing severe hypertension, and cases refractory to salt privation alone have shown no further benefit from the additional infliction of undernutrition or complete starvation.

4. *Refractory Cases, Temporary Benefits, and Delayed Benefits.*

Case No. 808. Male. American. Age 29. Married. Oil business. Admitted August 10, 1921.

Complaint: Dyspnea, loss of weight, dimming of vision in the left eye.

Family history: Father died at 79 of apoplexy. Mother died at 45 of strangulated hernia. One sister died at 37 of cardiac disease, another sister died at 67 of cardiac insufficiency with edema. One brother died at 62 of hypertension. One brother is living at 62 with rheumatism.

Past history: Does not remember having childhood diseases. Always healthy and strong as a boy. At age of 19 had severe jaundice following attack of malaria. Typhoid fever at 20. Four or five Neisser infections between ages of 20 and 27. In 1903 he was refused life insurance on account of some physical defect, but does not know exactly why. Three years later, however, he was accepted and has passed several other examinations since. Numerous Wassermann tests have been negative. Has always considered himself quite healthy. As a young man he did heavy manual labor, but for past 15 years has lived a rather inactive life as director of several corporations. Upon advice of his physician he had not used meat for the past three years, and other forms of protein had been closely restricted.

Present illness: In 1917 had severe epistaxis which lasted for four hours. A physician was called but the blood pressure was not taken and the patient was not informed of the cause of the trouble. A month

later there was gradual dimming of vision of the right eye. He consulted an ophthalmologist, who recommended that he have his blood pressure taken. The blood pressure was found elevated. For the past three years he has been short of breath, somewhat dizzy on exertion, and noticed that he became fatigued very easily. Vision in the right eye gradually grew worse. Eighteen months ago he had pain in the right eye, also flashes of light, and noticed that bright lights were surrounded by rainbow colors. The condition gradually grew worse. At this time the vision in the left eye became impaired and he could read only with difficulty. Diagnosis of glaucoma of the right eye and "retinitis" of the left was made. Six months ago the right eye was enucleated. Severe hemorrhage followed, which was controlled by the operator with great difficulty. Blood pressures during the past 18 months have ranged from 200 to 276 mm. systolic, 110 to 150 mm. diastolic.

Three months ago he suffered from frontal headaches for about one month. With this exception he has not suffered from headaches at any time in his life. For the past two years he has noticed slight swelling and puffiness of the ankles above the shoe tops at night. Nocturia one to two times per night for three or four years. His former weight was 203 lb. dressed. There has been a slow gradual decline for the past two years, and his weight three months ago was 173 lb.

Physical examination: Elderly adult male, with tendency to obesity, especially about the abdomen and neck. Height 5 ft. $10\frac{1}{2}$ in.; weight 163 lb. The skin and mucous membranes are somewhat pale. Muscles are thin and flabby. No evidence of jaundice. There is a suggestion of cyanosis of the lips, and superficial dilatation of the capillary vessels over the face. Eyes: right, artificial; left, sclera somewhat injected. Pupil is small but reacts to light and accommodation promptly. No exophthalmos. Slight photophobia. Eye-ground shows definite arteriosclerosis; the arteries are small and tortuous, and end abruptly in places. There are a few small hemorrhages scattered throughout the retina; the macular area is free, apparently normal. Vision 15-30. The whole of the retina is pale in color. Heart is slightly enlarged, and the apex beat is 1 cm. outside of MC line in the 5th interspace. Some increase in cardiac dullness on deep and superficial percussion. Increased retro-manubrial dullness. Blood pressure 238/130. Pulse 80 per minute. Brachial and radial vessels thick and tortuous. Temporal vessels markedly sclerotic. Aortic second sound loud and accentuated. Abdomen normal. Prostate gland slightly enlarged but not hard or tender.

Progress in the Institute: On admission, the patient was placed immediately on a rigid salt-free diet, without restriction of protein or calories. Judging from the first 24-hour urine analysis, he must have been fond of salt, since he excreted a total of 11 gm. On the second day the chloride decreased to 5 gm. Notwithstanding the strictest chloride privation, polyuria and nocturia continued (hyposthenuria), and the blood pressure and symptoms were practically unchanged up to discharge on August 24, 1921.

Progress after discharge: Upon return home he followed a rigid

salt-free diet until his detath on September 8, 1922. Blood pressures taken by his family physician were never below 200/120. In December, 1921, it was found 266/148. Vision in the left eye gradually diminished to almost total blindness three months before his death. There was no perceptible benefit from diet or any other treatment at any time.

Case No. 808

DATE 1921	NaCl in Diet gm.	URINE			BLOOD			Blood Pressure		Weight lb.
		Volume cc.	NaCl %	NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Urea mg. per 100 cc.	A. M.	P. M.	
Aug. 10	0	2600	.519	1.0	134	577	58	238/130		
" 11	0	2100	.239	5.0				212/130	240/146	
" 12	0	1850	.144	.26				202/150	200/130	163
" 13	0	2200	.140	.30				206/120	206/140	
" 14	0	2000	.024	.48				246/150	220/150	160
" 15	0	2250	.041	.92				210/130	208/130	
" 16	0	2000	.049	.98				200/130	210/130	160
" 17	0	2300	.008	.18				210/130	230/130	
" 18	0		.004					226/130	218/130	160
" 19	0	2250	.024	.54				224/130	214/130	
" 20	0							228/150	200/110	161
" 21	0	2300	.033	.75				226/130	220/130	
" 22	0	1500						248/140	230/130	161
" 23	0	2500	.010	.25	130	532	26	202/110	232/116	

Case No. 376. Female. Hebrew. Age 54. Married. Housewife. Admitted December 8, 1920.

Complaint: Shortness of breath, precordial pain, anesthesia of right side of the face, weakness, dimness of vision, irritability, nervousness and diabetes.

Family history: Irrelevant.

Past history: Practically negative except for poor vision, which has existed for the past 15 years. She has worn glasses for that length of time. She had no serious illnesses. She was always inclined to obesity. Her greatest weight was 184 pounds 15 years ago, but it has gradually dropped to 153 pounds during the past three years. Her diet has been excessive and she is inclined to overeat, especially carbohydrates and fat.

Present Illness: In October, 1917, she consulted a physician on account of shortness of breath, palpitation of the heart, ringing in the ears, and dizziness. Blood pressure reading made for the first time was found over 200 mm. systolic. A routine urine examination revealed sugar, although she did not complain of polyuria, polyphagia or polydipsia. Morning headaches, which came on at about 6 o'clock and continued until about 11, had appeared three months previously, but she had been inclined to disregard them. She also complained of sticking sensation about the heart, and pain which radiated down the left arm. Her physician prescribed a low protein diet, which consisted

chiefly of toast, cereals and fruit. Meat and eggs were forbidden, but she was permitted to use fish and chicken twice each week. Glycosuria did not subside on such diet. She continued on this diet until May, 1920, but during the time dyspnea and palpitation remained in evidence, and she suffered from cardiac distress and several anginal attacks. Shortness of breath on several occasions was sufficiently alarming for her to rest in bed for several days. Blood pressure readings averaged 210 mm. systolic. One month ago she had an acute attack of pain over the left eye, and anesthesia and formication of the right side of the face, which persisted for about six hours. It was accompanied by dyspnea and precordial pain. She was perfectly conscious and there was no evidence of aphasia. She became greatly alarmed and was afraid she was going to die. A physician was summoned and with the use of amyl nitrite and morphine the attack gradually subsided. She had a second similar attack two weeks ago and another yesterday. The body weight gradually fell 10 lb. in the past three years.

Physical examination: Moderately obese elderly female. Height 5 ft., 6 in.; weight 158 lb. The skin is anemic and has a peculiar pale gray color. Mucous membranes are anemic. Eyes: pupils are small; react slowly to light and accommodation. The conjunctivae are pale. She complains of cloudy vision and is unable to read a newspaper without the aid of glasses. The eye-grounds are pale and the arteries very small. No hemorrhages seen. Numerous yellow opaque masses are seen about the macula of the right eye. Teeth are in very poor condition. Considerable pyorrhea. Lungs normal. The P. M. I. is 1 cm. outside of MC line. Slight bulging with each systole. No thrills. Systolic murmur at the apex which is not transmitted outward. Aortic second sound accentuated and no murmur can be detected. Blood pressure 278/120. There is definite anesthesia surrounding the left eye. Abdomen: liver and spleen normal in size. Right kidney is palpable. No abnormal abdominal masses. All reflexes are hyperactive. Radials and brachials thickened and tortuous. The temporal vessels are firm and hard, and are seen as a wavy line over the temporal region. The urine showed specific gravity 1022, traces of albumin, numerous hyalin and granular casts, 2 per cent sugar, no acetone, and no diacetic; chloride 0.54 per cent.

Progress in the Institute: Patient was admitted at 8 P. M. with a blood pressure of 278/120. She was extremely nervous and restless and afraid to lie down to sleep, fearing that she was going to die. She complained of palpitation of the heart and slight precordial pain. The acute symptoms were relieved by codein and ice packs over the precordium. She was given a strictly salt-free diet of 40 gm. protein and 10 gm. carbohydrate throughout her stay in the Institute. Her body weight was reduced 7 lb. Glycosuria ceased entirely after 24 hours and remained absent, and the blood sugar was kept below 150 mg. per 100 cc. The continued undernutrition and rigid salt-free diet failed to reduce the hypertension and also failed to give any relief from the subjective symptoms. Palpitation, tinnitus aurium, irritability, nervousness, weakness and dizziness continued just as before admission. Blood

pressure readings remained at a dangerous level as shown in the table. The lowest reading obtained at any time was 184/125, with a general average of about 220 mm. systolic and 110 mm. diastolic. On December 24 and 27 two alarming anginal attacks occurred accompanied by dyspnea, apprehension, radiating pain down the arms, and sharp sticking pain around the heart. Blood pressures taken during the attack were over 225 mm. systolic and 125 mm. diastolic. She was discharged January 5, 1921 on a diet which was only approximate because of home conditions.

Progress after discharge: Three office calls were made after discharge, the first on January 17, 1921, when the blood pressure was 210/110. Glycosuria was absent, but there was hyperglycemia of 225 mg. per 100 cc. The diet had been followed very poorly, as indicated by the urinary chloride of 0.35 per cent. She complained of weakness, dizziness, tinnitis aurium, and clutching sensation over the precordium and heart. Other office calls were made February 2 and February 17, when the blood pressures were found 220/105 and 265/105 respectively. The symptoms continued unrelieved.

Case No. 376

Date 1920	Volume cc.	URINE			BLOOD			BLOOD PRESSURE	
		Grav. Spec.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.
Dec. 8	1300	1.022	.54	7.02					
" 9	915	1.022	.20	1.80	241	597	26	250/110	204/90
" 10	620	1.020	.04	.24				252/120	264/130
" 11	575	1.022	.02	.115				250/114	264/130
" 12	1000	1.018	.04	.40		540	50	218/104	
" 13	855	1.018	.04	.34				248/108	238/102
" 14	1610	1.015	.04	.64				238/104	250/105
" 15	1025	1.013	.02	.20				238/104	250/105
" 16	1975	1.014	.01	.31				222/80	228/80
" 17	1700	1.012	.02	.35	193	556	48	242/98	235/90
" 18	1250	1.013	.01	.31				222/82	235/90
" 19	1850	1.013	.03	.45				250/95	
" 20	2100	1.013	.08	.16					
" 21	2250	1.010	.01	.22	133	550	36	288/100	220/100
" 23	2210	1.007	.008	.17					
" 24	2375	1.009	.012	.17					
" 25	1625	1.012	.016	.26					
" 26	2075	1.010	.012	.24					225/85
" 27	2225	1.010	.016	.24	145			208/85	
" 28	2100	1.011	.012	.25					
" 29	1900	1.010	.033	.62	147				
" 30	2250	1.007	.016	.36					240/138
" 31	2650	1.009	.03	.70	149	564	28		
Jan. 1	2380	1.008	.016	.38					240/197
" 2	2250	1.007	.016	.36					220/102
" 3	2150	1.006	.016	.34				230/85	200/100
" 4	2750	1.007	.02	.55	127	536	36	228/95	

Case No. 52. Male. American. Age 45. Married. Broker. Admitted September 29, 1919.

Complaint: Occipital headaches intermittent in character, throbbing in head, insomnia, cloudy vision, nocturia.

Family history: Father died at 42 of heart trouble. Mother died at 62 of apoplexy. One brother has hypertension. One brother living and well.

Past history: Measles and chickenpox as a child. Mumps at 19 followed by orchitis. Scarlet fever at 12. Has always worked at high tension and led a dissipated life. He has over-indulged in rich foods and used alcohol often to excess for the past 25 years. Denies syphilis.

Present illness: Patient has been subject to headaches for 7 years. At first they were mild in character and disappeared quickly. Five years ago, while in the Rocky Mountains, had severe attack of headache accompanied by dizziness, which lasted for two weeks and necessitated his return to a lower altitude. Has had polyuria and nocturia for five years. Two years ago the diagnosis of hypertension was made. At the time he suffered with occipital headaches which were intermittent in character and often lasted for two to four days. During the attacks it was necessary for him to remain in bed. When the diagnosis was made he was given a low protein diet, nitroglycerine and potassium iodide. In the fall of 1918 he underwent a course of treatment which consisted of colonic irrigations, high frequently currents and violet ray. At the same time he was given a diet which consisted only of fruits, vegetables, nuts, and cereals. He obtained little relief under such treatment. Headaches have increased in intensity in the past six months and it was necessary for him to retire from business. Insomnia began six months ago. He suffered from throbbing at the base of the skull, occipital headache, tinnitus aurium and feeling of pressure over the scalp. His vision has gradually grown poorer, visual disturbances being manifested in the form of cloudy vision and haziness. He consulted an oculist, who diagnosed "retinitis" and gave him a change of glasses, which improved the vision but little. For the past two years blood pressures have ranged from 200 to 260 systolic, with diastolic pressures from 100 to 160. He has gradually grown weaker and tires very easily even on slight exertion. He gave up alcohol a year ago and has abstained from coffee and other stimulants, also from meat.

Physical examination: Fairly well developed adult male, showing evidences of loss of weight. Skin has marked pale ashen gray appearance. Mucous membranes of the pharynx and the conjunctivae are anemic. Skin over the hands is pale and pasty. Patient complains of severe headaches. He is restless and complains that noises and jarring intensify his pain. He has lost considerable sleep and complains of fatigue and weakness. Hair slightly gray; baldness over the frontal region. Eyes react slowly to light and accommodation. Pupils are pin-point in size but regular in outline. Examination by his oculist on the day of admission was as follows: "Considerable

swelling of the nerve head. The appearance of the fundus does not indicate a great deal of turgescence of the retinal vessels but the arteries are small and end abruptly. There are three small areas of exudate and two small hemorrhages in the left eye". Pharynx, ears and nose normal. The temporal vessels are thickened and palpable and show numerous plaeques. Radial and brachial arteries are thickened and tortuous. Lungs are normal. Heart enlarged 1 cm. to the right of the sternal border and 2 cm. to the left of the MC line. Aortic second sound is loud and booming. No murmur at the apex. Blood pressure 235/145. Abdomen negative. Reflexes hyperactive. No edema. Height 5 ft. 7 in. Weight 140 lb.

Progress in the Institute: From the history of the case and the physical examination, poor prognosis was evident, as nephritis and arterial changes were very marked and the plasma chloride low. During the first two days of institutional treatment he was given a diet which was as strictly salt-free as possible, with little change in the blood pressure readings.

On the third day a salt tolerance test was performed. Ten grams of sodium chloride was given by mouth. Blood pressure readings before administration of the chloride were 245/150. Two hours after administration the pressure had fallen slightly to 238/150, with increase in the plasma chloride concentration from 576 to 592 mg. per 100 cc. Beginning at the third hour the pressures gradually mounted to a maximum of 280/180 at the fifth hour. Headaches were intense. Vision was cloudy and hazy, and he suffered intensely from throbbing at the base of the skull. He became nauseated and vomited at the end of the fifth hour. He stated that the headaches were the severest that he had ever suffered. One-third grain of heroin and 1/8 grain of morphine were required to relieve him. Plasma chlorides continued to increase steadily to 620 mg. per 100 cc. at the end of the eighth hour. Although 10 gm. was given by mouth, only 3.7 gm. was excreted during the following 24 hours.

Following the test the diet was again made strictly salt-free. Although it was somewhat unpalatable at first, he soon became accustomed to it and did not complain of the absence of salt. There was slow gradual remission in pressures within a period of a month. From October 25 to November 23 he was entirely free of headaches, and blood pressures were the lowest recorded over a period of several years, averaging 172/100. He was very cheerful and encouraged by the progress. On October 29 he was examined again by his oculist, who reported less edema of the nerve head. Further hemorrhages had not occurred.

Progress after discharge: The patient was discharged on Nov. 24 to continue treatment under a dietitian at his home. He was given a diet of 50 gm. protein and unlimited calories. Numerous urine tests showed that he was excreting only trifling amounts of salt. At first he gained strength, transacted business and was much encouraged. Without apparent cause, he suffered relapse beginning about December 15. Headaches returned, accompanied by some precordial distress on exertion and a feeling of oppression over the frontal region. He

gradually and progressively grew worse. Headaches, fatigue and insomnia were constant, in spite of careful dietary control. Blood pressures steadily increased and averaged 220/140, with occasional readings as high as 235/150. On January 19 a spinal puncture was performed. The fluid was under no increased pressure; negative for globulin; cell count normal; Wassermann test negative. On February 1, 1920 he went to Florida accompanied by a nurse and dietitian. His condition was critical. Blood pressure taken the day of departure was 240/150. One week after arriving in Florida he became drowsy and stuporous, and edema of the the ankles and face developed. The urine became scanty, and little relief was obtained by the use of digitalis and various diuretics. He was given hot packs and the usual treatment, including two bleedings of 300 and 500 cc. respectively. Nothing altered the continuous hypertension and growing unconsciousness. Small muscular tremors developed but no general convulsions. Death occurred with unconsciousness and weakness Feb. 14, 1920.

Case No. 52

Date 1919	URINE			Plasma NaCl. mg. per 100 cc.	Blood Urea mg. per 100 cc.	BLOOD PRESSURE		REMARKS
	Volume cc.	Spec. Grav.	Total NaCl gm.			A. M.	P. M.	
Sept. 29	2380	1.009		575	55			
Oct. 30						235/145		McLean Index 19.
1								Phthalein test 27.4%
2	722	1.017	1.04	620	61.0	240/160	246/160	
3	1021	1.015	2.46			240/140	254/140	
4	800	1.016	3.77	572	51.0	230/130		10 gm. salt by mouth
5	1000	1.017	2.50			250/145	248/136	
6	510	1.022	.30	546	60.4	246/140	258/160	
7	980	1.020	2.27			255/150	252/160	
8	1410	1.013	2.72	538	66.2	250/150	256/146	
9	460	1.018	.27	485	50.0	250/150	252/158	
10	515	1.018	.10	470	60.2	228/140	224/135	McLean Index 10.8.
11	510	1.017				220/130	224/90	
12		1.016				200/130	232/130	
13	830	1.014	.40			228/145	230/130	
14	790	1.016	.23			220/150	218/140	
15	540	1.014				200/110		
16	875	1.012				208/120	235/140	
17	780	1.014		490	54.4	215/140	220/150	McLean Index 4.7.
18	545	1.013				204/130	200/120	Phthalein test 25.8%
19	250	1.015				216/120	182/130	
20	625	1.017				210/130	210/140	
21	410					200/120	212/120	
22	780	1.015				214/140		
23	690	1.016		427	59.4	210/145	210/140	McLean Index 13.45.
24	560	1.016				194/125		
25	700	1.015				198/125	178/110	
26	700	1.016				218/140	174/90	

Case No. 52 (continued)

Date 1919	URINE			Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	BLOOD PRESSURE		REMARKS
	Volume cc.	Spec. Grav.	Total NaCl gm.			A. M.	P. M.	
27	630	1.015				170/98	176/110	
28	500	1.019	1.00			174/110	182/110	
29	490	1.018	1.41	489	59.2	206/110	210/120	McLean Index 20.
30	400	1.015	1.53			190/120	188/110	
31	520	1.015	3.09			212/130	164/110	
Nov.								
1	510	1.014	0.68			174/110	176/100	
2	420	1.015	0.324			180/120	166/100	
3		1.013				188/100		
4	420	1.013	0.56			190/100		
5	480	1.014	0.739			170/106	172/110	
6	560	1.013	1.07			172/104	178/110	Phthalein test 35.5%.
7	370	1.012	0.62			182/108	175/109	
8	480	1.014	1.8			176/105	175/108	
9	200	1.017	0.942			182/110	175/110	
10	570	1.013	1.38			178/108	189/115	
11	570	1.012	1.59			177/110	195/118	
12	470	1.009	.885			160/ 98		
13	930	1.021	4.29			158/ 80	195/110	
14		1.014				176/ 95	198/120	
15		1.012				174/110	210/120	
16	680	1.012	2.35	559		206/115	190/120	
17	930	1.009	3.27			204/110	215/ 90	
18	780	1.013	3.44			204/110	190/113	
19	2560	1.006	4.32	571	30.2	215/130	190/100	
20	810	1.008				200/120		
23							225/130	
24		1.014					200/140	

Case No. 1070. Female. American. Age 56. Married. Housewife, Admitted February 13, 1922.

Complaint: Nervousness, irritability, emotional strain, shortness of breath.

Family history: Father died at 71 of stomach trouble. Mother at 80 is living and well. One sister and two brothers are living and well. There is no history of diabetes, obesity or high blood pressure in the family. One child is living and well. Patient has had no miscarriages.

Past history: Patient was always in good health and remembers no childhood or acute diseases. At the age of 20 to 30 she had headaches associated with nausea and vomiting, which disappeared later in life. Teeth have always given considerable trouble, but she has never suffered from pyorrhea. She had numerous sore throats before tonsillectomy twenty year ago. She has been short of breath on exertion for the past fifteen years, but not sufficiently to cause alarm. She attributed the condition to steady increase in body weight before that time. She has never suffered from palpitation of the heart. Appetite was always

good, but recently she has had indigestion with belching of gas after eating, which was relieved by sodium bicarbonate. She has no history of gallstones or jaundice. Menses began at the age of 12, always regular and normal. One year ago she was given X-ray treatment to produce artificial menopause. Periods have not appeared since. Maximum weight was 164 lb. two years ago. She voluntarily restricted diet, and reduced her body weight about 30 lb. Previous to that the diet was an ordinary one. She is not fond of any special form of food.

Present illness: Three years ago a blood pressure reading was made during the course of routine physical examination, and was found to be 244 systolic. She had noticed increasing dyspnea on exertion, although she was not alarmed. During the past three years she has been more irritable and nervous than formerly. The least possible excitement brings on nervous attacks, and she is much more emotional. She has always been an active leader among her friends and was engaged in considerable club work, which she has had to give up during the past two years on account of fatigue and nervousness. She has had numerous flushes, especially in the face and neck, the attacks coming on quickly and without warning, her face becoming hot and the skin having a peculiar burning sensation. She has not suffered from headaches. Her condition has become steadily worse during the past year.

Physical examination: Patient is a well nourished woman past middle age. Hair is somewhat gray. Skin is loose and there is evidence of previous loss of weight. Eyes react normally to light and accommodation. Nose and ears normal. There are several crowned teeth. Tonsils have been removed. No palpable glands in the cervical region. Thyroid is palpable but not enlarged. Lungs are resonant throughout, no rales heard. Heart does not appear enlarged; on percussion there are no shocks or thrills. Aortic second sound is accentuated and ringing; no murmurs heard at the apex. Blood pressure 220/130. Pulse rate is regular. Vessel walls are normal. Abdomen normal. Height 5 feet, 2 inches; weight 137 lb.

Progress in the Institute: The blood pressure was slow in responding, and no real relief of subjective symptoms was experienced until the patient had been approximately three weeks in the Institute. The chloride intake was kept at the minimum which would prevent privation symptoms, which represented about 1 gm. per day or slightly less in the urine. The plasma chloride was constantly high. The blood pressure, though appreciably reduced, never became normal. The subjective symptoms were relieved. After March 1 flushes, nervous and emotional attacks were practically absent, and long walks were taken without undue fatigue or breathlessness. This same condtion has continued under home treatment.

The benefit in this case has been delayed and incomplete but nevertheless marked and lasting. Another example of delayed response to treatment, in which normal blood pressure was finally restored, is found in case No. 1080 (p. 525).

Case No. 1070

DATE 1922	URINE			BLOOD			Blood Pressure		Weight lb.
	Volume cc.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.	
Feb.									
4				131	620	22			
5		.239					220/130	200/120	
6	1600	.107	1.71				180/120	196/100	137
7	1450	.053	1.55				180/100	180/110	
8	1500	.070	.742					186/100	137
9	1200	.029	.840				180/100	200/100	
10	1700	.043	.495				160/120	192/120	136
11	1200	.045	.516	121	610	39	190/114	190/100	
12	1300	.062	.585				200/100	192/110	135
13	1550	.082	.961				198/120		
14	1100	.082	.902				210/120	180/110	135
15	1300	.058	.754					192/110	
16	1300	.066	.858				186/108	200/104	134
17	1400	.058	.812				180/102	210/114	
18	1400	.072	1.00	209	597	28	180/110	190/100	134
19	1350	.062	.837				202/110	190/106	
20	1250	.062	.775				192/112	192/100	134
21	1500	.037	.555				200/130	200/130	
22	1350	.095	1.28				162/90	190/100	134
23	1200	.095	1.14				184/100	192/100	
24	1650	.062	1.02				190/120	196/120	134
25	1600	.082	1.31				202/120	190/110	
26	1700	.086	1.48				180/100	180/96	133
27	1250	.107	1.33	142	597	26	190/120	170/96	
28	1400	.041	.574				160/100	180/100	133
Mar.									
1	1506	.066						170/100	133
2	1700	.066	1.12				180/110	180/106	
3	1500	.070	1.05				184/100	180/110	134
4	1750	.053	.927				210/130	190/110	
5	1200	.091	1.09				170/104	190/110	134
6	2200	.031	.682	166	597	32	170/100	190/110	
7	1800	.024	.432				180/110	182/108	133
8	1500	.024	.360					182/104	
9	1650	.029	.478				166/102	176/106	
10	1800	.022	.396	138	597	20			134

Though some cases are genuinely refractory, presumably because of the extent or character of the organic changes, many unnecessary failures will be encountered if the salt restriction is not continued faithfully for a sufficient length of time. Case No. 1080 (p. 525), and case No. 188 previously published[78], illustrate delayed results which were ultimately very satisfactory. Though benefits are necessarily transitory in certain cases.

these benefits appear real nevertheless in the sense of a prolongation of both life and comfort; and stubborn persistence in the treatment, based on belief in its theoretical advantage whether practical results are evident or not, has led to an unexpectedly satisfactory outcome in a few cases which were regarded through considerable periods as entirely hopeless.

5. *Salt Privation Symptoms; Causes of Occurrence and Absence.*

Symptoms of salt privation have been mentioned in some cases (e. g., Nos. 974, p. 479, 2041, p. 486), so that no special examples are required. The symptoms themselves are characteristic, but they may appear in different patients under widely different conditions.

A salt supply may be conceived to be necessary for maintaining either a flow of salt through the body into the urine, or merely a certain salt concentration in the blood. In the latter event, renal impermeability for salt might reduce the salt requirement, because the damming up of salt in the blood might suffice for osmotic purposes and for providing a supply to the tissues. Clear cut results along these lines seem to be not obtainable. In a general sense it seems to be true that persons with peristently high renal chloride thresholds, maintaining their plasma chlorides above 590 mg. or even above 600 mg. per 100 cc. on the strictest possible chloride privation, are able to endure such privation indefinitely without serious symptoms. Patient No. 53, (p. 524), however, whose plasma chlorides are always above 600 mg. and sometimes above 610 mg. per 100 cc., seems to be kept in a state of slight chronic asthenia by the continuously salt-free diet. The addition of 1 or 2 grams of salt daily makes her feel definitely stronger and happier, but within a few days the rise of blood pressure and attendant symptoms of intense headache, dizziness and prostration necessitate a return to the rigid diet. In the same general sense, it is probably true that patients with impairment of the function of salt excretion can endure salt privation better than normal persons. On the other hand, there are wide differences in the plasma chloride concentrations at which different patients show privation symptoms. Some of them developed serious symptoms at plasma chloride levels far higher than those on which others remained entirely free from symptoms. Experiments by Bliss, to be published shortly, suggest that dif-

ferences likewise exist between different normal persons, and that some of these may withstand almost as strict chloride deprivation as any hypertension or nephritic patients. Complicated relations of general capillary permeability, or the equilibrium between chlorides in the plasma and in the tissue fluids and cells, seem to be an undefinable third factor. Illustrations may be obtained not only in comparisons between different patients but in comparisons of the same patient at different times. For example, a patient with edema may have low chloride concentrations in the blood plasma and edema fluid; privation symptoms may remain absent on salt-free diet until the edema fluid and its chloride have been excreted through the urine, and then with the onset of these symptoms the plasma chlorides may be found higher than the original level. It is obvious that this same factor, under conditions of "invisible" edema or under any other conditions, can abundantly explain the non-parallelism between blood chlorides and blood pressure which seems to have proved confusing to some writers.

Physicians who have not witnessed privation symptoms have not used salt-free diets, and their reports concerning the influence of chloride restriction upon hypertension are indecisive. These symptoms form no essential feature of the treatment, and with experience they can often be avoided and almost always checked in their incipiency. For example, when the blood pressure in any case falls to normal on salt-free diet within a few days, it is generally safe to conclude that the condition is relatively mild, that small additions of salt can be tolerated, and that without them privation symptoms will soon appear . Accordingly, without waiting for any suggestion of symptoms, a ration of 0.5 to 2 gm. of salt may be begun, and trials of the salt tolerance made as usual. Although many patients require less than 2 gm. of sodium chloride daily, our experience confirms the general belief that 2 gm. is sufficient for any individual, that any symptoms occurring on this ration are not due to lack of salt, and that any greater quantity than this is a luxury to be permitted only with great care. In severe cases, privation symptoms may begin to appear before the reduction of blood pressure is satisfactorily accomplished, and the rationing of salt so as to balance privation symptoms against hypertension symptoms is then a delicate but feasible

problem. The most difficult cases are those in which the pressure is only slightly reduced by chloride restriction which causes privation symptoms, but the best clinical result in these actually hopeless cases is afforded by a chloride allowance which gives a mixture of mild privation symptoms and mitigated hypertension symptoms. A few attempts to substitute sodium chloride in such cases with other compounds such as hydrochloric acid, sodium bicarbonate, potassium chloride, or potassium iodide have not yielded any practical encouragement, chiefly because of the hopeless organic conditions in these refractory cases.

6. *Influence of Small Additions of Salt.*

Irrespective of the height of either the systolic or the diastolic pressures, cases may in one sense be considered mild in proportion to the quantity of salt which can be taken without harm. Generally the response to treatment in such cases is more rapid and complete and the prognosis brighter than in cases with lower salt tolerance. Some patients, for example, may show marked hypertension and attendant symptoms with a chloride intake of 10 to 20 gm. and apparently normal conditions with an intake of 4 or 5 gm. daily. Obviously, the salt ration is not to be set by any arbitrary standard but is to be worked out to meet the individual need of each patient. Cases with high salt tolerance have been almost wholly absent from the present series, because they mostly show the variability of the mild or incipient stage; either the elevation of pressure is not great, or it changes greatly under various minor influences, such as the nervous state, and the temporary exacerbations and remissions have been a cause of confusion in the literature and impair the usefulness of such cases as objective evidence. In the majority of the severe and established cases selected for this series, in which the pressures may indeed be raised by exciting influences but under no conditions fall below a markedly abnormal height, the chloride privation must be more stringent and small allowances may have a powerful influence.

It was noticed in case No. 2105 (p. 470) that the plasma chloride and blood pressure rose when 2 gm. salt was added to the diet, and the patient had to be sent home on salt-free diet. Patient No. 53 (p. 524) has been mentioned as one who must live continuously without salt, and the addition of 1 gm. or less daily

suffices for a gradual elevation of pressure and distressing symptoms. Case No. 656 (p. 514) is also illustrative.

The following is a brief summary of case No. 429, in which the chloride variations have been due to the patient's carelessness with diet. This case is instructive also as proof that the results are not due to accidents or environment, for the exclusion of the 2.2 gm. of salt which had crept into the diet at home relieved the pressure and other symptoms without other change in the habits. The more serious condition which resulted from 5.2 gm. of salt daily was similarly relieved.

Case No. 429. The patient is an American housewife, aged 51 years. There are several cases of renal and vascular disease in the family. The patient has suffered from dizziness and headache for the past ten years. In 1916 she underwent appendectomy, cholecystectomy and gastroenterostomy. The systolic blood pressure then was 275. Since then it has not been below 220 or 230, according to the physicians who constantly observed her. Admitted Feb. 4, 1921.

Physical examination was negative except for arteriosclerosis and retinitis.

The record under salt-free diet is shown in the following table:

Case No. 429

DATE 1921		Urine NaCl gm.	Plasma NaCl mg. per 100 cc.	Blood Pressure		REMARKS
				Syst.	Diast.	
Feb.	4	7.90	608	236	108	Admitted. Headaches.
	9	.82	589	210	100	Symptoms relieved.
	17	.61	618	178	100	Feels well.
	24	.48	601	188	104	Feels well. Discharged.
Mar.	18	2.20	589	232	131	Has made mistakes with diet. Has headaches and dizziness.
Sept.	16	traces	573	150	110	Symptom-free, since correcting mistakes in diet.
Dec.	9	0.90	520	137	78	Working hard and feeling well on careful diet.
1922						
May	13	5.20	596	236	140	Recently careless in diet. Headaches, blurred vision.

When small additions of salt fail to cause a proportional increase of urinary chlorides, and instead give rise to increase of plasma chlorides and blood pressure, the salt intake must obviously be kept below these quantities. The individual salt

ration must therefore be worked out, sometimes in fractions of a gram, between the quantity causing retention and hypertension symptoms as an upper limit and the quantity causing salt privation symptoms as a lower limit. As either the retention or the privation symptoms may require from several days to several weeks for their appearance, the establishment of the correct relation often requires both time and care. Institutional treatment is important, for one reason, because both patient and physician often become discouraged under the inaccuracies of home treatment. It will be observed that the conditions of salt exclusion for controlling hypertension are often much more exacting than for reducing edema, and this is undoubtedly the most important cause for failures in the use of the treatment and for the prevalent skepticism concerning its benefits.

7. *Cardiac Symptoms and Complications, and the Use of Salt-Free Diets in Pure Cardiac Cases.*

Cardiac death is recognized as one of the common terminations of hypertension. The familiar and dreaded signs of a failing heart may appear while the pressures are high or even increasing, or may be attended by a fall either of the systolic pressure alone or of both systolic and diastolic pressures. In addition to the frequent functional insufficiency of the heart valves, organic valvular lesions are not a rare complication of hypertension. Analogy suggests trial of salt privation for certain cardiac cases without hypertension.

Case No. 814. Male. American. Age 55. Married. Stationary engineer. Admitted August 12, 1921.

Complaint: Shortness of breath, oppression over the heart, palpitation.

Family history: Father died at 40 of pneumonia. Mother died at 45 of "asthma". No other history of hypertension, Bright's disease, cardiac disorders or diabetes in the family.

Past history: Had whooping cough and measles at the age of 10. Twenty years ago had pleurisy in the right side, which incapacitated him for two weeks, but has had no return of the trouble since. Wassermann test performed three months ago was negative. Has lived rough working life and used alcohol at times to excess.

Present illness: One year ago he began to be short of breath on exertion, and had occasional dizzy spells, which he attributed to becoming over-heated. About the same time he noticed increased thirst, and began to urinate one or two times during the night. He was inclined to disregard the condition until four months ago, when he began to have numbness in the palm of the right hand with a sensation of

formication and chilliness. He was given a low protein diet, digitalis and potassium iodide with no relief. He had numerous attacks of dyspnea, especially on exertion, and at times the vision was blurred, and the outlines of small objects were indistinct. He had no headache. He has noticed a feeling of oppression over the heart, and some throbbing extending to the veins in the neck, especially at night after retiring. He has gradually grown weaker, and his appetite has failed. He belches considerable gas when he indulges in too much food. Blood pressure for the past three months has averaged 200 to 240 systolic. Increasing dyspnea during the past week has forced him to sleep propped high on pillows.

Physical examination: Height 5 ft. 8 in.; weight 147 lb. Well developed adult male, with signs of acute heart failure. Hair slightly gray. Slight puffiness under the eyes. Pupils are small and regular in outline, and respond to light and accommodation. Tongue is coated; there is fetid odor on the breath. Mucous membranes of the pharynx are hyperemic

Case No. 814

DATE 1921	URINE			BLOOD			Blood Pressure	
	Volume cc.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.
Aug. 12	1600	.480	7.68					220/140
" 13	1350	.25	3.37				200/120	200/140
" 14	1400	.177	2.98				210/140	210/130
" 15	1400	.177	2.98				200/100	208/100
" 16	2000	.058	1.16				190/ 90	190/110
" 17	2100	.042	.88				190/100	190/100
" 18	1400	.051	.71				190/100	
" 21	1600	.041	.656	125	532	20	190/120	192/120
" 22	1300	.053	.689				190/90	180/90
" 23	1400	.041	.654				170/76	
" 24	1700	.025	.425				188/126	218/120
" 25	1400	.029	.406				170/120	220/120
" 26	1300	.058	.044				190/120	
" 27	1800	.058	.044				170/120	190/110
" 28	1300	.049	.637					
" 29	1700	.049	.833				180/110	190/120
" 30	1000	.053	.530				180/120	186/106
" 31	1700	.095	1.610				170/104	210/80
Sept. 1	700	.041	.285		540	54	180/100	205/150
" 2	800	.062	.496				178/130	180/90
" 3	800	.074	.672				174/120	174/120
" 4	1300	.049	.630				170/80	198/120
" 5	1850	.049	.906				160/70	
" 6	1200	.020	.240				170/100	186/100
" 7	1300	.055	.715				172/90	152/98
" 8							158/80	170/90
" 9	800	.055	.440		556	40	179/90	184/100

and there is considerable pyorrhea alveolaris. There is constant slight dyspnea at rest, and lips are cyanotic. Slight exertion causes acute breathlessness. Coarse mucous rales over lungs. There is slight heaving over the precordium with each systole. The point of maximum impulse is 2½ cm. outside the MC line in the 6th costal interspace. Faint systolic thrill at the apex. Marked retro-manubrial dulness. Marked increase of cardiac dullness on deep and superficial percussion. Systolic murmur at the apex which is transmitted posteriorly. Aortic second sound is loud and booming. Heart rate irregular, and there are numerous abortive systoles. Blood pressure 220/140. Abdomen flat. Liver edge about 1 cm. below costal margin. Spleen not palpable. Extremities and skin are normal. No edema. No tortuous arteries are visible on the forehead, but the radials and brachials are thickened.

Progress in the Institute: Salt-free diet was the only treatment employed, without digitalis or any other drugs. Great relief followed the excretion of 7.68 gm. of salt in the first 24 hours. The body weight fell 3 lb. in 2 days, and the skin lost its puffiness and became wrinkled. Within 3 days the patient was walking freely about the grounds without dyspnea or weariness, was sleeping soundly in the horizontal position, and was free from thirst, nocturia and all other subjective complaints.

Progress after discharge: The patient resumed his regular work, but abandoned diet because of ignorance and unfavorable environment. He was treated for relapses in several hospitals without success, and cardiac death occurred March 15, 1922.

Case No. 372. Male. Irish-American. Age 50. Married. Labor union official. Admitted November 23, 1920.

Complaint: Blurred vision, dizziness, shortness of breath, palpitation of the heart.

Family history: Mother died at 36 of pneumonia. Father died at 50 of the same disease. No history of tuberculosis, cancer or diabetes, but sister aged 48 has high blood pressure.

Past history: Numerous sore throats have been attributed to the fact that he has always worked hard as a mechanic and been exposed to cold and cold water daily. Eye-sight was good until three years ago, when he began to wear glasses on account of gradual blurring of vision. Pneumonia at the age of 20; he was sick four months. Never had night sweats or loss of weight. Fifteen years ago articular rheumatism of the right hip kept him at home from work ten days. Four years ago he passed a life insurance test as a first-class risk. Had used alcohol in excess up to four months ago. Denies syphilis.

Present illness: The present illness began eighteen months ago with shortness of breath. On going up steps or attempting any form of heavy labor, he notices a choking sensation with clutching at the throat and chest. He is also dizzy, and a few weeks after the onset developed a cough. Weakness is a prominent symptom, particularly in the knees and legs. He stopped work for three months, during which time he became more comfortable, but has not been able to perform heavy labor since. One year ago dyspnea and palpitation became extreme. He had swelling of the limbs which lasted for three weeks, and was

treated with iodides and digitalis. For the past year he has had feelings of oppression over the precordium. Dyspnea has progressed. He suffers especially at night, and has had numerous coughing spells with shortness of breath and palpitation. Vision is gradually growing worse, and he notices that newspaper print and small objects appear blurred and confused. Occasionally tinnitus aurium has been present and interfered with his sleep at night. Nocturia, 4—6 times each night. Puffiness about the ankles has been present for eight or nine months. Three weeks ago symptoms became alarming on account of constant shortness of breath and asthmatic attacks. The appetite has been poor and capricious. Abdominal distress has occurred after each meal. On exertion he becomes dizzy, and objects in the room seem to revolve.

Physical examination: Well nourished muscular adult male in distress, with anxious appearance, lips purple and cyanotic, and breathing more rapid than normal and occasionally slight cough. The eyes react well to light and accomodation. Eye-grounds are pale. Arteries and veins are smaller than normal; disc outlines can be only poorly defined. Ears and nose are normal. Marked pyorrhea alveolaris. The throat is red and the tonsils large and contain numerous crypts, but no exudate can be expressed. Heart: no venous pulsation can be made out in the neck but only most forcible carotid pulsation can be seen. Pulsation can be made out in the episternal notch. There is bulging and heaving over the whole precordium and the P. M. I. cannot be definitely localized, but as best can be made out is 1 cm. outside the MC line. Left border of heart is 14 cm. from the midline, the right border 6 cm. from the midline. Left axis is 19 cm. Heart rate is irregular, as is pulse. Cardiac beat 104 per minute; pulse deficit 55 per minute. There is a loud systolic murmur at the apex, which is transmitted outward into the axilla. Aortic second sound is loud and booming. No murmur over aortic region. Blood pressure 240/120. The lungs are negative except for moist rales at the bases posteriorly. Liver and spleen not palpable. Radial and brachial arteries thickened and palpable. Enormous varicose veins on both legs. Reflexes present. The urine was scanty, dark, and contained albuminin, casts and blood cells. Height 5 ft. 10 in.; weight 160 lb.

Diagnosis: Mitral insufficiency; regurgitation; auricular fibrillation; cor bovinum; dyspnea, edema.

Progress in the Institute: On admission, the patient was given an ordinary diet with the exception of sodium chloride. No drugs were used, and no rest beyond the patient's own inclination. By November 26 he was definitely more comfortable and cyanosis had disappeared. The pulse beat at the wrist was still irregular, the pulse deficit being 47 per minute. Blood pressure readings varied, ranging from 150 to 165, with occasional strong beats coming through at 170. He breathed more comfortably, and dyspnea on exertion was much less. By November 28 the pulse deficit had decreased to 4 per minute, and the pulse was regular and slow. Clinically he was in much better condition and was able to move about without shortness of breath or palpitation. He endured a salt-free diet without difficulty and had no symptoms of

salt privation. The skin, which on admission was tense and unwrinkled, became loose and numerous folds and creases appeared. On December 4 the blood pressure was 155/92. The heart rate and rhythm were almost regular. Cyanosis remained absent. There was no pulse deficit, and there was less bulging and heaving over the precordium. He remained at the Institute until December 21, 1920, when he was discharged with blood pressure 160/80 and without edema or cyanosis.

Progress after discharge: On account of the patient's home conditions and difficulties in following a constantly accurate diet, he has met with several reverses in the past two years. On the whole, however, the diet has been sufficiently well regulated to avoid any real relapses or critical developments. Numerous 24-hour urine specimens analyzed during the past 2 years have shown an average of about 3 gm. NaCl. He has been able to carry on his work continuously. Blood pressure readings have averaged 180/100. With over-exertion he be-

Case No. 372

DATE 1920	URINE				BLOOD			Blood Pressure A. M.
	Volume cc.	Spec. Grav.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	
Nov. 23	700	1.017	.70	4.9	140	577	28	180/70
" 24	1300	1.017	.44	5.7				170/70
" 25	705	1.018	.24	1.69				
" 26	855	1.023	.20	1.71				160/110
" 27	1310	1.012	.14	1.83				
" 28	815	1.017	.08	.65		581	26	
" 29	750	1.020	.09	1.05				168/80
" 30	1350	1.017	.06	.81				160/90
Dec. 1		1.012	.06			564	30	170/90
" 2	1030	1.014	.06	.61				
" 3	1275	1.017	.10	1.27				
" 4	1250	1.018	.14	1.75				155/92
" 5	1100	1.013	.10	1.10				
" 6	1825	1.011	.16	2.92				
" 7	1175	1.014	.18	2.11				
" 8	550	1.017	.04	.22				
" 9	1700	1.013	.04	.68				140/90
" 10	450	1.020	.04	.18				162/80
" 11	1390	1.012	.04	.55				145/80
" 12	1400	1.013	.14	1.96	123	560	32	
" 13	775	1.011	.02	1.55				144/90
" 14	375	1.017	.06	.22		544	20	144/92
" 15	630	1.014	.04	.25				
" 16	675	1.016	.03	.24				
" 17	950	1.014	.25	.47				
" 18	750	1.014	.20	1.50				
" 19	190	1.017	.09	.17				
" 20	850	1.015	.02	.17				160/80
" 21	300	1.025	.09	.27	123			

comes dyspneic, but otherwise he has had no labored breathing or asthmatic attacks. The heart has been irregular at times with slight pulse deficit, but on the whole there is excellent compensation.

According to our experience, it is not true that the best treatment for impending cardiac failure consists in attempting to drive the heart to carry an overload under which it must sooner or later break down in spite of any stimulation. In a choice between cardiac stimulants and salt restriction, the latter is greatly to be preferred in hypertension cases. Obviously, no such exclusive choice is necessary, and one of the great advantages of salt-free diet is that it is not only beneficial in cases in which digitalis has failed, but soon enables digitalis to act effectively in these same cases. Cases in which a terminal fall of blood pressure has occurred, unless the condition is entirely hopeless, respond favorably to salt-free diet with or without heart stimulants, thus showing that the action of the diet is something more than a mere mechanical reduction of blood pressure.

Hearts with organic valvular disease, which are laboring under the additional burden of hypertension, receive enormous relief from the diet treatment. In proportion as the organic cardiac factor is large, and the renal or functional factor is small, the possible benefit of dietary functional relief shrinks. Neverthless, edema, oliguria and dyspnea are cardinal symptoms of cardiac failure in general. It should be recognized in an equally general sense that salt restriction reduces the tendency to edema and eases both circulation and respiration. Dry diet, which is so often recommended for the treatment of cardiac cases, cannot be rationally carried out without corresponding salt restriction, and the latter generally makes rules concerning water intake unnecessary. In the same way undernutrition may be obviated for patients who seriously need the strength obtainable from adequate food. Though the effectiveness of both muscular and metabolic rest is unfortunately limited it seems worth suggesting that the latter, in the sense of salt restriction, has received inadequate attention in the routine treatment of heart disease at all stages.

At the same time, strict caution is necessary in the use of salt restriction for cardiac cases with or without hypertension, as the weakness and prostration resulting from too extreme privation may prove dangerous. In the pure cardiac condi-

tions, it is probably never necessary to reduce the sodium chloride ration below the safe level of 2 gm. For cases with hypertension this degree of relief may be entirely inadequate and the best results may be obtainable only from the strictest chloride privation. The closest clinical and laboratory observation may then be required for guidance.

8. *Cardiac asthma, angina pectoris, and vascular crises.*

These circulatory complications, closely related to the preceding topic of cardiac conditions, are illustrated by the following cases.

Case No. 1258. Male. American. Age 58. Married. Manufacturer. Admitted October 16, 1922.

Complaint: Shortness of breath, weakness and exhaustion.

Family history: Mother died at 60 of diabetes; was very stout. Father died at 52 of pneumonia. One brother died of cardiac decompensation. One sister, living and well, is obese. One child, aged 20, is living and well. Patient has been married 28 years. Wife in good health; has had no miscarriages.

Past history: The usual childhood diseases, and diphtheria at the age of 14. His tonsils have always given him a great deal of trouble; become inflamed easily and he has been incapacitated several days each winter on account of tonsillitis and quinzy sore throat. Has never had pneumonia or pleurisy. Always a hearty eater, in fact, he has indulged himself too much in rich foods. Maximum weight was 242 pounds three years ago; average weight was 215 pounds; he always attempted to keep the weight at this level by regulation of diet. Two years ago had series of severe boils around the waist and axilla. They came on spontaneously, and appeared in series for about two months. Three months ago he had recurrence of boils. In addition to those on the body, a large one appeared on the back of the neck, which required operation.

Present illness: Always healthy and strong until three years ago, when he began to be short of breath on exertion. Up to this time he had been able to do heavy manual labor and drive his car many miles each day, but he noticed that even the exertion incident to steering his automobile brought on shortness of breath. On stooping over or attempting to carry even small parcels dyspnea appeared. He did not suffer from dizziness or headaches. He was admitted to the Johns Hopkins Hospital and treated for a period of two weeks. The blood pressure was over 200 systolic. He was advised to reduce his weight, which he did, bringing it from 244 lb. to 190 lb. He gave up meat and eggs and other rich proteins. Two months ago dyspnea became distressing in spite of this program, and was accompanied by stabbing pains about the heart. He had numerous asthmatic attacks which were worse at night. Insomnia developed and he began to have fantastic dreams. It became necessary for him to go to bed on account of edema which appeared and increased rapidly. Protein in the diet was still closely

restricted, and he lived chiefly on cereals, bread and starches, taking only chicken in small quantities once each week. In spite of bed rest and prohibition of salt, the entire condition steadily grew worse. The body weight steadily rose from 190 lb. to 217 lb. in six weeks. A week ago orthopnea, sleeplessness and delirium appeared. Cough, in his asthmatic attacks, brings up thick tenacious sputum. He has no headaches, but flashes of light with dizziness are present on exertion. Blood pressure readings have been averaging about 150 systolic for the past five or six weeks.

Physical examination: Large stout man in acute distress, with anxious expression, breathlessness and cyanosis. He is unable to lace his trousers completely on account of swelling of the abdomen. Eyegrounds show very hazy discs, vessels very small and obscured in places on account of edema of the retina. Maculae appear normal. Vision is very poor. He is able to read only large headlines of newspapers, and unable to read small print even with the aid of glasses. There is anemia of the conjunctiva and the mucous membranes. Teeth are in fair condition. The skin is pale and pasty. No wrinkles can be seen anywhere on the body; the skin of the face, chest and abdomen looks to be tense with fluid. He complains of dizziness on exertion, and says that he is conscious of each heart beat. Lungs are clear, except for rales at both bases posteriorly. Heart is enlarged to 2 cm. on the left. P. M. I. is 1½ cm. outside the MC line. No shocks or thrills. No abnormal pulsations seen over the precordium. No murmur at the apex. No adventitious sound over the aortic region. Blood pressure 140/110. Radial arteries are palpable but not sclerotic; temporal vessels are tortuous and palpable; no placques can be made out. Abdomen is distended with fluid. Liver edge 2 cm. below ribs in MC line, soft but not tender. Reflexes present. Height 5 ft. 9 in. Weight 219 lb.

Laboratory: Blood urea 54, plasma chloride 564, plasma sugar 173 mg. per 100 cc., during digestion. Wassermann negative. Urine contained albumin and casts.

Progress in the Institute: The supposedly salt-free diet followed by the patient at home contained about 4 gm. sodium chloride. Owing to the acute danger, the salt exclusion in the Institute was unusually strict, some of the vegetables and meats being boiled out with distilled water. Protein was given liberally. Digitalis, which had failed to give relief, was continued. The table shows how in 6 days about 50 gm. salt was excreted and corresponding weight lost. By the time of discharge on November 5 edema and all the symptoms had disappeared, and the patient was walking a mile or more daily and sleeping without disturbance every night. The blood pressure rose at first as the heart gained strength, then fell to a normal level.

Progress after discharge: The patient followed the diet at home carefully with only a few mistakes. Blood pressure readings were never found over 160, the general average being 140 systolic. A urine specimen was analyzed on December 18. The volume was 900 cc., specific gravity 1014, NaCl 0.082 per cent, total 24-hour NaCl

0.738 gm. A second specimen was analyzed on January 5, the volume being 800 cc., NaCl 0.070%, total NaCl 0.616 gm. There has been no return of asthmatic attacks or other symptoms, except to a slight extent which called attention to the mistakes mentioned. Correction of the mistakes gave complete relief. It is still necessary for the patient to take an occasional 4-day course of digitalis, otherwise myocardial weakness makes itself apparent in the form of lassitude and breathlessness on slight exertion. With these precautions he has been able to resume business duties, which he thought he had given up forever.

Case No. 1258

DATE 1922	NaCl in Diet gm.	URINE				Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	Blood Pressure		Weight lb.
		Vol. cc.	Spec. Grav.	NaCl %	Total NaCl gm.				A. M.	P. M.	
Oct.											
16	0									140/110	
17	0	1800	1012	.239	4.3	173	564	54		150/90	219
18	0	3000	1011	.247	7.41	129	552	36	130/100	178/112	
19	0	3080	1012	.264	8.0				160/80		
20	0	2600	1015	.470	12.4	148	581	29	160/90	164/118	209
21	0	2210	1014	.507	11.2				158/100	162/88	205
22	0	1520	1015	.497	7.5				140/80	160/106	202
23	0	1350	1013	.062	0.8				130/90	160/96	200
24	0	1600	1014	.124	1.9				130/88	160/102	199
25	0	1300	1016	.097	1.2				132/100	130/96	
26	0										
27	0	500	1020	.247	1.2						197
28	0										
29	0	1200	1020	.148	1.7	146	589	34	140/86	140/70	196
30	0	1320	1010	.144	1.8		601	24	150/78	150/80	
31	0	1200	1011	.136	1.6				130/80	150/80	196
Nov											
1	0	1000	1010	.173	1.7				130/90		
2	0	730	1017	.103	0.7				130/80	130/80	193
3	0	1160	1016	.078	0.9	105	573	20	136/90		194
4	0	700	1016	.086	0.6						192

Case No. 1144. Female. American. Married. Age 40. Housewife. Admitted May 5, 1922.

Complaint: Fatigue, exhaustion, headache in the morning, pain over the heart, radiating pains down the arms.

Family history: Father died at 50 of Bright's disease. Six uncles on her father's side died of Bright's disease. Patient has three sisters; one has had high blood pressure for twelve years, and the other two are in good health. Patient has been married for 20 years, and has two children living and well. Has had one miscarriage.

Past history: Measles, mumps, chickenpox as a child. Pneumonia twice, but each time it ran a mild course. In August, 1923, one month after the birth of her last child, she began to complain of sick head-

aches, loss of appetite and drowsiness, and her skin had a peculiar yellowish tinge. This condition continued for two months, and the headaches were distressing. She noticed that her complexion became less florid, and the skin seemed pale and pasty. Albumin was found in the urine at that time accompained by a few casts. Her doctor told her that she had "chronic nephritis." Average weight was 125 lb., maximum weight 135 lb. at the age of eighteen. She has always lived an active life, and is athletically inclined.

Present illness: Her real symptoms and complaints date from September, 1920, when she began to suffer from palpitation of the heart and pain over the precordium. Blood pressure was found to be 190/140. She was put to bed for two weeks, but she was allowed light graduated exercise after the pressure had fallen to 145 systolic two weeks later. She remained in this condition for three months, when there was a return of the symptoms. She suffered from irritability, fatigue, insomnia and extreme nervousness. The morning headaches became frequent and have increased in severity. Large doses of amyl nitrite and potassium iodide have given little benefit.

On February 28, 1922, she was awakened at 5 A.M. with severe pain around the heart, dyspnea, throbbing and palpitation. Occipital headache was intense. Her physician was called immediately, and on arrival found the heart enlarged 2½ cm. outside the MC line in the fifth interspace; pulse 140 and blood pressure 247/130. She became cyanotic and more dyspneic for several hours. The pulse became irregular and weak. She remained in this condition for about sixteen hours, after which time the pain gradually subsided. She was kept in bed for four weeks. Blood pressure readings ranged from 200 to 240. During the past two months she has suffered daily from anginal attacks, morning headaches, fatigue and weakness. It has been necessary for her to give up her social activities with which she was very much engaged.

Physical examination: Well developed adult female, of muscular build. Bony structure normal. Skin has a peculiar pale muddy tinge. The checks have only a slight color. Eyes: pupils normal in size and shape, and react normally to light and accommodation. Eyegrounds are pale, and the arteries smaller than normal. The veins are slightly dilated where they are crossed by the arteries. There are no excavations or placques on the retina. Maculae normal. Chest is well formed and lungs are normal. On percussion the left border of the heart extends 1½ cm. outside the MC line. The M.P.I. is in the fifth interspace. There is a definite precordial bulge with heaving. There are no thrills. Aortic second sound loud and snapping, accompanied by rough systolic murmur. No murmur at the apex. Blood pressure is 242/150. Radial arteries are thick and easily palpable. Reflexes present and equal. Height 5 ft. 3 in., weight 113 lb.

Laboratory findings: Blood urea 24, plasma chloride 556, plasma sugar 108 mg. per 100 cc. Patient's 24-hour urine specimen, specific gravity 1015, contained 4.9 gm. of NaCl.

Progress after admission: A liberal diet, including ordinary quan-

tities of protein, fat and carbohydrate was prescribed, with salt restricted to the closest possible extent. She was encouraged to take a moderate amount of exercise, which was enjoyed, since all forms of activity had previously been restricted. Within six days the patient felt considerably relieved from her former symptoms, and suffered less from precordial distress and anginal attacks. Blood pressure readings gradually decreased, but at no time during the treatment were they normal, and the diastolic readings were always in excess of 120 mm. A poor prognosis in the case was evident from the beginning on account of the marked sclerosis and low plasma chloride. On a restricted salt diet her progress was encouraging, since the headaches were less severe and on many days were absent entirely. On May 24 she began to suffer from the usual symptoms of salt privation—weakness, pain in the legs, loss of appetite and nausea. She ate practically no breakfast, and beginning with the noon meal she was given an allowance of one gram of NaCl for the 24 hours. The salt privation symptoms

DATE 1922	NaCl in Diet gm.	URINE			BLOOD			BLOOD PRESSURES		Body Weight lb.
		Vol. cc.	Spec. grav.	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.	
May 5	0	1450	1015	4.90	108	556	24		242/150	
" 6	0	1500	1013	2.77				212/130	190/110	113
" 7	0	1400	1013	1.33				202/140	176/130	
" 8	0	1550	1011	1.27				170/126	162/100	113
" 9	0	1050	1010	.609	106	560	26	210/160	182/100	113
" 10	0	800	1016	.528				180/110	182/120	113
" 11	0	1150	1015	1.138				180/110	180/120	113
" 12	0	1050	1012	.388				180/122	170/120	113
" 13	0	1150	1016	.667				170/118	168/120	
" 14	0	1700	1010	.901				164/104	170/108	114
" 15	0	1700	1010	.731	127	622	24	180/110	170/108	114
" 16	0	1800	1010	1.116				174/108	170/100	114
" 17	0	1550	1009	.821					160/106	
" 18	0	1300		1.066				170/100	182/120	115
" 19	0	1600	1011	1.248	118	618		172/108	174/120	
" 20	0	1400	1009	.980				170/102	170/100	
" 21	0	1300	1015	.962				180/130	170/120	
" 22	0	1300	1012	.962				180/118		116
" 23	0	1300	1013	1.339				168/110	170/112	
" 24	0	1300	1012	1.339				180/120	190/122	117
" 25	1	1250	1010	2.015	112	587	36	170/120		117
" 26	1	1300	1015	1.872				176/120	178/120	116
" 27	1	1200	1011	1.824				170/122	168/120	116
" 28	1	1350	1011	2.281				180/120		116
" 29	.75	1500	1010	2.415	115	589	26	180/128	242/160	
" 30	0	1000	1010	1.440				190/130	178/120	
" 31	0	1300	1012	1.06					200/130	115
June 1	0	1600	1010	1.18				200/140	190/130	
" 2	0							206/140		

were promptly relieved. Appetite immediately returned, and the pain in the legs disappeared. The general improvement was only temporary. On May 28 she had a sudden anginal attack, accompanied by dyspnea, palpitation and excruciating pain in the left breast, which radiated down the arms. The attacks occurred two or three times daily during the following week. The pressure became elevated and was not controlled by close salt restriction. On May 29 she experienced one of her most severe attacks. She was put to bed for a period of three days.

The patient was discharged on June 2, 1922. For one week after her return home she was free of anginal attacks and cardiac pain. Blood pressures ranged from 160 to 190 systolic. She then began to suffer from dyspnea, weakness and cardiac pain at irregular intervals of one month. She adhered closely to a strict salt-free diet, and several 24-hour urine specimens showed an output of one gram or less. The condition has since remained about the same. The blood pressure is lower than formerly and the acute attacks less frequent, but the improvement is only partial.

Case No. 656. Male. American. Age 62. Married. College professor. Admitted July 19, 1921.

Complaint: Mental confusion, ability to think of words but not to speak them, paresthesia of the face, high blood pressure.

Family history: Mother died at 60 of stomach trouble and asthma. Father died at 60 of pneumonia. One brother, aged 60, has high blood pressure. Two brothers have heart trouble. One brother and two sisters living and well. Patient married 30 years. Wife and two daughters living and well.

Past history: Had measles, mumps, whooping cough and scarlet fever when a child. Between the ages of 25 and 35 he suffered from headaches, which he attributes to over-study and improper glasses. Four years ago he was operated on for infected antrum, which was drained and has caused no trouble since. Cardio-respiratory history negative. At the age of 40 he had typhoid fever of severe type. He was in bed for five weeks and lost 35 lb. in weight. For ten years he has noticed that it has been necessary for him to void at night, especially if he has insufficient covering and becomes chilled. Nocturia has increased gradually during the past ten years. Smoked pipe for 40 years. He has been a teacher all his life. Present body weight is 166 lb., which he has maintained for the past ten years. Maximum weight was 185 lb. 30 years ago.

Present illnes: He has known he has had high blood pressure for six years, but had never taken treatment or considered it of any consequence. Four months ago he suddenly had mental confusion and aphasia. He experienced no unusual sensation except that he was unable to speak and could not think what he wanted to say. He was clear mentally and able to recognize persons, printed words and objects but was unable to articulate distinctly. He was told afterward that his language was jargon. His right hand and arm were numb and there was paresthesia of the right side of the face and the hand. There was slight loss of muscular power. He walked to his home and went

to bed, and after a few hours felt perfectly well and was able to articulate distinctly. A physician who was summoned found the blood pressure 185/110, temperature normal, pulse 72, respirations 20. The physical examination was negative. Reflexes were present, and the heart rate and rhythm normal. He lost only a few days from his work. A month later, while in class room, he experienced return of the same symptoms. The attack was more severe and there was considerably more loss of sensation in the face and arms, and the right leg was also involved. The vision was not impaired and he experienced no pain. Similar attacks were experienced in May of 1922, and two very slight attacks in June which lasted for about half an hour. Speech returned as promptly as it disappeared. The urine has been free from albumin, casts, and sugar. His physician advised rest, light diet, mental relaxation, saline purgatives and drugs—salol and chloral, 15 grains each day. Drug therapy was discontinued after one month. During the past five months pressures have ranged from 170 to 225 systolic.

Physical examination: Well developed large adult male, well proportioned except for slight excess of fat on the abdomen. He is mentally alert and shows no evidences of distress or confusion. Hair is slightly gray. Eyes: pupils react normally to light and accommodation. Slight arcus senilis. Patient is myopic. Eye-grounds are normal except for slightly tortuous arteries which are smaller than normal. No evidences of hemorrhages, choroiditis or retinitis. Maculae normal. The temporal vessels are thickened and tortuous, and numerous firm plaeques can be felt along the course of the vessels. Radial and brachial arteries are likewise sclerotic and tortuous. No enlarged glands of the neck. Thyroid normal in size. Lungs normal and resonant throughout. No impairment on percussion. No rales or adventitious sounds. Heart rate regular. Slight retro-manubrial dullness. No shocks or thrills. On percussion the heart is enlarged 1 cm. to the right of the right sternal border and 1½ cm. to the left of the MC line. No bulging or heaving. Aortic second sound is accentuated. No murmur can be heard at the apex. Blood pressure 204/126. Liver and spleen cannot be palpated. No abdominal tenderness. Reflexes present and equal. The urine is free from albumin and casts. Height, 5 feet, 11 inches. Weight 166 lb.

Progress in the Institute: The diet was restricted only in salt. The body weight was not reduced. During the 2 weeks' stay in the Institute there was no return of vascular spasms as manifested by aphasia or paresthesia. There was marked decrease in urine output, especially at night, the patient no longer rising at night, though formerly he had voided 3 or 4 times nightly.

He tolerated the salt-free diet well until July 30, when he experienced some loss of appetite and weakness. He found it necessary to force himself to take a normal amount of food. Since the pressures were normal, 2 gm. of sodium chloride was added to the diet daily. The extra salt was excreted promptly and was accompanied by increase in urine output. He was discharged from the Institute

August 1, 1921, and instructed to continue taking foods which were strictly salt-free and add 2 gm. of sodium chloride, which was to be accurately weighed.

Progress after discharge: After discharge the patient reported at regular intervals for office calls, and has remained thoroughly faithful to diet. He is clinically in better condition. Blood pressures have remained low except when unintentional errors in diet have been made. During the year and a half which has elapsed, he has had only one return of aphasia, the attack being of mild degree. He was given a leave of absence from his college and spent a year in Italy, where he was able to secure a diet which was fairly low in salt. On September 15, 1921 he returned for an office call. Blood pressures showed considerable increase over the ones taken at the time he was discharged from the Institute, namely 195/115. He had restricted salt in the diet closely, and the 24 hour urine specimen showed a total of 2.3 gm. The plasma chloride showed a marked increase over former tests taken in the Institute, indicating a considerable retention of salt. Analyses were as follows: Blood urea 28 mg., plasma sugar 132 mg., plasma chloride 622 mg. per 100 cc. He was advised to discontinue the use of the 2 gm. of added salt.

On October 11, 1921 he returned for a second office call. The total 24 hour chloride excretion was 1 gm. and blood analyses showed considerable improvement, as follows: Blood urea 34, plasma sugar 120, plasma chloride 581 mg. per 100 cc. Blood pressure was 160/100. He felt well, and had no return of vascular symptoms.

Case No. 656

DATE 1921	NaCl in Diet gm.	URINE				BLOOD			Blood Pressure		Weight lb.
		Vol. cc.	Spec. Grav.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Urea mg. per 100 cc.	A. M.	P. M.	
July											
19		695									
20		1275		.33	6.20						166
21		1375		.06	.82	109	589	22			
22		1000		.11	1.1					204/126	
23		1200		.08	.96				160/102	172/110	166
24		1450	1.026	.07	1.01				178/110	174/110	
25		800		.07	.56				166/120	162/106	
26		750	1.024	.10	.75				188/100	136/100	165
27		700		.06	.42				130/ 80	158/100	
28		550	1.020	.11	.60	107	536	16	158/100	150/ 80	166
29		775		.06	.42				132/ 96	150/100	
30	2	1400	1.020	.09	1.26				120/ 80	160/110	167
31	2	1250	1.021	.13	1.62				140/ 90	148/ 80	
Aug.											
1	2	1350	1.021	.14	1.89				142/ 90	146/ 90	167

A third office call was made on October 28, 1921. He felt well on the restricted salt diet, and had no complaints. The blood pressure, after walking into the office, was 150/80. The 24 hour urine specimen of 1000 cc. contained a total of 0.9 gm. of sodium chloride. The plasma chloride remained low at 573 mg. per 100 cc.

From November 2, 1921 to November 15, 1922 he was in Europe. He had several blood pressure readings made while there, and at no time did they exceed 175 systolic.

On December 1, 1922 he returned for another office call; he had been away from home the greater part of the two weeks preceding, and had taken foods which were known to contain salt. Blood pressure was 200/140. The urine specimen showed total NaCl 7.68 gm., and the blood analyses were as follows: Blood urea 32, plasma sugar 141, plasma chloride 597 mg. per 100 cc.

He was advised to take every possible precaution with diet, to restrict the salt in the diet and to avoid the use of it in cooking. He remained at home and followed the instructions as closely as possible. On January 15, 1923 the blood pressure was 166/85, and the total 24 hour urine specimen showed 1.2 gm. NaCl.

This patient's condition is evidently determined by the chloride content of his diet, and his chloride tolerance is less than 2 gm. per day.

So-called cardiac or renal asthma, though one of the most distressing accompaniments of hypertension, is also one of the easiest to relieve by salt restriction. Through the courtesy of Dr. Robert Cook we were enabled to make examinations of several patients with true bronchial asthma, including some who responded satisfactorily to protein tests and therapy and others whose trouble was doubtful in origin and difficult of control. The investigation seemed interesting both because of the comparison with cardiac asthma and also because of the apparent disturbance of salt and water metabolism in the reactions to foreign proteins. No tendency to chloride retention was found in any of the true asthmatics. Likewise, a few cases of bronchial asthma observed incidentally in this Institute have received no benefit from salt-free diet.

Angina pectoris is necessarily a difficult and dangerous condition, because its basis is so largely organic. From the few cases seen, we believe that accurate chloride restriction offers better relief than any other single measure, though it naturally does not interfere with the use of drugs or other customary treatments.

The control of the vascular crises, which are a prominent feature of some cases, is in proportion to the general success of the salt-free diet in the individual instance. A typical

result is that the patient may appear better for several days or weeks; then one of the acute attacks, with elevated pressure and attendant symptoms, occurs and creates doubt of any genuine improvement; the attack, however, is apt to be milder and briefer than those previously experienced, and is followed by a more marked remission; subsequently, in the course of months of strict treatment, the patient gradually becomes capable of greater activity for longer periods, while the crises lessen progressively in number and severity. The ultimate success varies widely in different cases, from the most fortunate ones in which the attacks cease altogether, to the most refractory cases in which continuance of the attacks is one of the signs of failure. In general, it is important that these supposed vascular spasms, which have been attributed entirely to nervous and other mysterious factors, are largely influenced by the chloride ration.

9. *Hereditary, Endocrine and Other Influences.*

The thyroid may presumably play a similar part in hypertension as in diabetes, namely not as a direct cause but as an aggravating toxic influence. We have seen two cases complicated with slight hyperthyroidism. The hypertension was mild (175-160 mm. systolic, 100 diastolic) but was very slightly influenced by chloride restriction, confirming the impression that some extra agency was at work. Benefit could probably have been expected from partial thyroidectomy, but operation was declined.

Cursory attention may here be given to polycythemia, because the associated hypertension has sometimes been attributed to increased viscosity of the blood due to the high corpuscle content, and the condition itself may possibly be regarded as a disturbance of the blood-forming organs or of some unknown apparatus of corpuscle regulation. A number of cases in this series have shown abnormally high red cell counts, but statistics cannot be given because the counts were made in comparatively few cases. The following illustration shows that polycythemic cases are similar to others in their chloride metabolism and response to chloride restriction, though the polycythemia itself persists, as though it were a complication rather than an essential part of the condition. The observations seem to add to the evidence against viscosity of the blood as a cause of high blood pressure.

Case No. 2207. Female. American. Age 55. Married. School superintendent. Admitted December 5, 1922.

Complaint: Dyspnea on exertion, polyuria, pruritus vulvae, weakness, loss of weight.

Family history: Mother died at 73 of cirrhosis of the liver. Father died at 32 of pneumonia. One brother died of pulmonary embolism at 77; 2 brothers living and well. Patient married one year.

Past history: General health always excellent, except 12 years ago when she developed sudden swelling of the glands in the right cervical triangle, which necessitated complete resection. She does not know the exact cause of the adenitis. Maximum weight 162 lb. 1 year ago; lowest, 118 lb., is present weight.

Present illness: In February 1922 had pruritus vulvae which was persistent and distressing. She also began losing weight and felt weak and tired all the time. The symptoms continued for a month until diagnosis was made. She has lost 44 lb. in the past year. The diet has been closely restricted in carbohydrate. She has been weak and fatigued all the time. For two years she has been slightly dyspneic on exertion, but she has never had anginal attacks or palpitation. She has known her blood pressure was high for two years. Her complexion has always been ruddy and for 4 years she has noticed her lips have been purple. She drinks unusually little water or other fluids.

Physical examination: Adult female of large stature, who shows evidence of loss of weight. Her skin shows a deep brown tinge but no real jaundice. The face is very high complexioned and ruddy, and the lips are of a deep purple color. The whole face is suffused and somewhat cyanotic. She is dyspneic after climbing a flight of stairs. Mucous membranes and conjunctivae normal in color. Lungs clear. Heart normal in size and shape. No murmurs at the apex or aortic area. Blood pressure 190/100. Liver is enlarged 2 cm. below costal margin, but not tender. No general glandular enlargement. The patient is weak and complains a great deal of weariness and fatigue. The first blood specimen drawn appeared unusually concentrated and clotted very quickly in spite of the fact that the usual amount of oxalate was used. A second specimen was drawn, and also had a tendency to coagulate. After centrifuging fifteen minutes, only a small quantity of plasma was obtained. The red cell volume was roughly estimated at 90%. The red cell count on admission was more than 10 million. All blood analyzed since admission has shown these peculiarities. Height 5 feet, 6 inches. Weight 118 lb.

Progress in the Institute: Glycosuria and hyperglycemia were readily controlled by the usual dietary measures and her diabetic condition proved relatively mild. Her food tolerance finally exceeded 1800 calories after about 6 weeks of treatment. On admission she was put on a strictly salt-free diet. The blood pressure readings within a few days decreased to fairly low values. The patient improved clinically and gained in strength and endurance. Plasma chloride determination on entrance showed a low value of 536 mg. per 100 cc.

On the 4th day she was urged to drink more water but found it difficult, and there was little change in the 24 hour urine volume. Red cell counts changed but little, averaging 8,500,000. All blood specimens were thick and viscid, and yielded but little plasma after centrifugalization.

Case No. 2207

	DIET			URINE				BLOOD				Blood Pressure		
DATE	Protein gm.	C. H. gm.	Total Calories	Vol. cc.	Sp. gr.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	Red Cell Count	A. M.	P. M.	Body Weight lb.
3	30	5	200											
4	30	5	200	1050	1052	.322	3.38	326	536	17	10,780,000	190/98	190/100	118
5	30	5	200	1300	1011	.074	.96					160/90	160/84	118
7	30	5	200	1200	1014	.102	1.22				8,076,000	160/102	152/100	115
8	50	5	200					173		24	8,870,000	164/100	160/100	
9	30	5	200	1000	1014	.152	1.52							114
10	35	7	200	1100	1015	.144	1.58					162/100		
11	45	10	200	1000	1017	.177	1.77	211			8,540,000	160/100	162/100	112
12	45	10	200	1200	1012	.110	1.32					170/102		
13	45	10	200	1400	1012	.078	1.09				8,340,000	174/102	172/102	111
14	45	10	200	1000	1015	.074	0.74	171	552	26		160/100	168/104	112
15	45	10	200	1250	1010	.041	0.51					168/102	170/100	110
16	45	10	200	1500	1011	.041	.61					164/104	160/100	
17	55	10	900	1300	1010	.052	.68					162/96	168/100	110
18	55	10	900	1200		.027	.32	187						
19	55	10	900	700		.107	.75					170/100	162/90	110
20	55	10	900	1300	1011	.058	.23				8,540,000	160/90	166/92	
21	55	10	900	900	1011	.027	0.24					140/90		111
22	55	10	900	1000	1013	.033	0.24	178	543	26				
23	55	10	900	1700	1011	.029	0.49							
24	60	15	1200	1100	1016	.310	0.34							

No other endocrine influences have been observed in any sense modifying the nature or the prognosis of cases. Nervous factors, which are commonly emphasized in the literature of hypertension, have been mentioned in a number of the cases already described, but it will be noticed that sucessful dietary treatment relieved the nervous symptoms, indicating that they were the result rather than the cause of the hypertensive state.

Hereditary cases have responded to treatment like the non-hereditary, and therefore do not constitute a separate type any more than in diabetes. The same has been found true of the cases which are observed in women about the time of the menopause. There is no valid reason for connecting the ovaries in any way with these cases or with blood pressure in

general. Hypertension is found in fully an equal number of men at about the same age, without any cessation of their sexual functions; and the women in question show the usual evidences of the renal basis of their hypertension. The following family group is interesting for throwing light on these questions.

Case No. 63. The patient is a Jewish housewife, aged 59 years. Her parents and probably several other relatives have had hypertension or nephritis.

The personal history is unimportant. She has four living children, and finished the menopause 15 years ago. She has been feeling more and more weak and unwell in an indefinite fashion since that time, but had no diagnosis or treatment until June, 1919, when she became completely incapacitated by dizziness and weakness. The physician who was then called found very high blood pressure, and sent her to the country for a complete rest. As she was no better after several

Case No. 63

DATE 1919	Plasma NaCl mg. per 100 cc.	Blood Pressure		Body weight lb.	REMARKS
		Systolic	Diastolic		
Oct. 3	620	240		120	Admitted bedfast; believed dying.
" 6	596	190	130	100	Much more comfortable.
" 9	567	182	129	100	Up in chair for short time.
" 20	600	166	129	85	Up all day; beginning to walk.
Nov. 1	578	140	130	80	Discharged in better health and spirits than for several years past.
1920					
Mar. 19	605	230	130	105	Well for several months. Recently careless with diet; symptoms returned.
Apr. 3	580	170	130	80	Salt-free diet followed at home has relieved symptoms.
1921					
Jan. 27	610	204	124	110	Pressures have been low and symptoms absent until past two or three months when she became careless with diet. Readmitted to Institute.
Feb. 6	576	188	129	00	Discharged feeling well.
1922					
Jan. 12	608	190	132	140	Again remained well until recently careless with diet. Readmitted to Institute.
Feb. 19	580	168	136	86	Discharged comfortable.

weeks, another physician was called, who continued the rest treatment and also prescribed a very limited, low protein diet. In August the patient returned home and continued to spend her entire time in bed because of dizziness and fainting on attempting to stand. She was first seen in consultation on September 16, when the blood pressure was 220/130. The patient was then transferred to a hospital under the care of another consultant for the purpose of the strictest possible bed rest and diet and drug treatments. October 3, being unimproved, she entered this Institute.

The essential features of the physical examination were advanced arteriosclerosis and senile changes, moderate retinitis, and threatening heart failure. The blood pressure was 240/120. Her record on a salt free diet is shown in the condensed protocol on page 521.

Case No. 96. This patient, aged 40, is a daughter of patient. No. 63, and came for examination because of headaches and urticaria Nov. 1919. The past history was unimportant, except that she has had three children, and had albuminuria during the last pregnancy. The albumin is said to have disappeared after confinement and she has felt well. Examination was negative except for albuminuria and casts, blood urea 44 mg. and plasma chlorides 620 mg. per 100 cc. The blood pressure was 170 systolic, 96 diastolic. A nearly salt-free diet, moderately restricted in protein, was prescribed at home. The headaches were relieved, but the patient considers herself well and has not come for further examinations.

Case No. 93. Male. Hebrew. Age 10. School boy. (Grandson of patient No. 63 and son of No. 96). Seen November 22, 1919.

Complaint: For three years he has been under a physician's care for intermittent attacks of nausea and dizziness, which come on a short time after meals and last about 30 minutes. Occasionally he would vomit. The attacks would leave him weak and prostrated. Throbbing headaches are always associated with the attacks, and usually persist for a half hour or more. He has suffered these seizures at approximately monthly intervals for the past three years. He has been on a diet which was normal except for red meats. At no time has he suffered from diarrhea. He has used considerable quantities of salt. The diagnosis of petit mal was made by one of the leading children's specialists of New York.

Physical examination: Well nourished boy of 10. The skin is of a peculiar yellow color, but there is no jaundice. Eyes, ears, and nose normal. Chronic inflammation of the right tonsil. Lungs normal. Heart normal except for a marked respiratory arrhythmia. Abdomen slightly protuberant. The liver is palpable and slightly tender. Spleen and kidneys not palpable. Blood pressure 100/60. Red blood cells 4,130,000; white blood cells 4,600. Blood urea 24, plasma sugar 102, plasma chlorides 612 mg. per 100 cc.

On salt-free diet at home, the attacks stopped promptly and completely. On January 7, 1921, the boy was seen again. He had increased considerably in height and weight, and had had no more of the former attacks. Salt had been closely restricted in the diet. The

blood pressure was 90/75, plasma chlorides 576 mg. per 100 cc. December 1922, the boy has gained markedly in height and weight, and has not suffered any return of symptoms, though salt has gradually been restored to the diet. No further analyses have been obtained.

Here it will be noticed that the grandmother developed hypertension symptoms about the menopause, though it is improbable that the condition originated at that time. The daughter's nephritis was diagnosed earlier, but had it been neglected the general disturbance of health at the time of the menopause might well have led to a diagnosis then and created a false impression. The small boy is of interest as the sole observed instance in which an epileptoid condition resulted from chloride retention. Pediatricians recognize a "spasmophilic diathesis" caused by a disturbance of salt metabolism[79]. It would be well for salt-poor diet to be tried in any such cases, and also in any in which fasting seems to relieve epileptic or other convulsions.

Various questions of normal plasma chloride standards, early diagnoses, and prophylactic treatment must also be raised by such investigations. As hypertension is so prevalent among the older population, a large predisposed element must exist among the younger classes. Thus far, these candidates for hypertension have been recognizable only in so far as they have been found to show more or less tendency to elevation of blood pressure in physical examinations[80]. In this Institute, examinations of some thirty supposedly healthy nurses and dietitians between the ages of twenty-five and thirty-five revealed abnormal pressures of 150 to 160 systolic in two cases, the elevation being apparently chronic in one and produced only temporarily by excitement in the other. Such women may perhaps go on without symptoms until about the menopause, and then a false interpretation be placed upon the disturbances. It is an interesting question whether investigations will show abnormalities of the chloride economy in persons who are still supposedly healthy, and whether such departures from normal will be specially numerous in families with hereditary hypertensive tendencies. The earlier the tendency to hypertension can be recognized, the better should be the opportunity for prophylaxis by restriction of the chloride intake.

10. *Influence of infection.*

It is assumed that in acute nephritis with hypertension, due to scarlatina, tonsillitis, etc., the direct vascular injury by the intoxication is the most important element. Cure of the infection is therefore the principal means for lowering the pressure, and diet, though not without influence, must be ranked as secondary. Any intercurrent infection in the course of a chronic hypertension may likewise be regarded as an aggravating influence, which will more or less modify the results of diet treatment. Two cases showing different effects of gallbladder infections may serve as examples.

Case No. 53. The patient was an American housewife aged 63 years, with negative family history. She was well up to the time of menopause, then, at the age of 44, began to suffer from attacks of weakness, dyspnea, palpitation and dizziness. These symptoms were similar to those which subsequently accompanied her hypertension, but they ceased at the age of 48 after a dilatation and curettage, and no blood pressure readings were made. In the same year the patient's back was broken in the region of the 12th thoracic vertebra, and she may have sustained internal injuries. She was incapacitated for a year, and slight deformity with limitation of movement remains permanently. A year later she was seriously ill with diphtheria, followed by partial paralysis, passing off after 6 months. About a year later she was ill for 3 weeks with typical gallstone symptoms; several less severe and definite attacks have occurred since. From that time onward she has been increasingly incapacitated by violent headaches, tinnitus, vertigo, weakness, and palpitation. The diagnosis of hypertension was made 10 years ago, and for the past 5 years the blood pressure has never been found below 200 mm., and twice during attacks was above 300 mm. She has undergone prolonged treatment with the usual bed rest, drugs, low protein diets, catharsis and bowel irrigations. She has always used salt in excessive quantities.

At her first examination, September 22, 1919, moderate cardiac enlargement and arteriosclerosis and slight retinitis were the significant findings. There was nocturia, and the 24-hour urine volume was between 3 and 4 liters. The blood analyses and renal function tests were normal, except for plasma chlorides of 640 mg. per 100 cc., and a chloride threshold about 610 mg. Salt-free diet without any other change in her habits or place of living gave prompt relief, so that within 3 days symptoms were greatly diminished and the blood pressure remained below 200 mm. By October 7 the pressure had gone down to 144/75. This relief continued most of the time up to 1921, but there were two outstanding peculiarities. First, on the strictest salt-free diet the plasma chloride was generally above 600 mg. per 100 cc., never below 590 mg. per 100 cc. One gram of salt in the diet sufficed to bring back hypertension and accompanying symptoms, but the patient never felt any ill effects from the strict salt privation, unless perhaps

a slight lack of strength. Second, she was seriously troubled with indigestion and constipation, and was subject to numerous acute attacks characterized by diffuse abdominal pain, vomiting, intense headaches, stupor, and hypertension of 210 to 230 mm. Sedatives, purgation and bleeding were found to be the only means of relief. Finally, in April 1921, operation was decided upon, chiefly on the basis of the definite gallstone history. The thickened gall-bladder was found tightly contracted upon a single cholesterol stone the size of a pigeon's egg, and was removed. Dense adhesions involving the liver, stomach and duodenum were broken up. The patient has since remained free from the abdominal attacks and from hypertension, except for occasional elevations to 160 or 170 with some minor infection such as a cold. She remains a semi-invalid, on account of weakness due to arteriosclerosis and the consequences of her former infections. Her chloride threshold is as high as before, strict salt-free diet is still necessary, and addition of salt to the diet invariably causes a return of hypertension and accompanying symptoms.

Case No. 1080. Female. American. Age 53. Married. Housewife. Admitted March 5, 1922.

Complaint: Dyspnea on exertion, hot flushes of the face and neck, occasional swelling of the feet, floating specks before the eyes, tenderness and pain over the gall-bladder.

Family history: Father died at 75 of apoplexy. Mother died at 85 of heart trouble. One brother living and well at 53. No sisters. Patient married twice. First husband died of apoplexy at age of 50. One child living and well. One miscarriage. Second husband is living and well at 57. There is no history of diabetes in the family.

Past history: Had whooping cough, measles and mumps in childhood. At the age of 13 she had diphtheria of severe type, followed one week after the onset by pneumonia, which ran the usual course. Has never suffered from headache or dizziness until recently. Never had trouble with the ears or throat. She has worn glasses for 2 years. Subject to colds and cough each winter. Last year she had chronic cough with considerable tenacious sputum for about two months, terminating with pleurisy, which was very painful and lasted about ten days. Never had dyspnea or edema until the present illness. Appetite always good and bowels regular. Six years ago had sudden pain and tenderness in the epigastrium accompanied by nausea and vomiting. The attack lasted for 12 hours. She was slightly jaundiced, especially over the face and neck, and the sclerae were yellow for about three weeks. Since this time she has suffered from attacks of indigestion and has belched gas. Bowels have been irregular and it has been necessary for her to take numerous purgatives. In October, 1921, she had sudden return of pain over the epigastrium and gall-bladder region accompanied by jaundice, nausea and vomiting. Stools were white in color. X-ray showed six large stones in the gall-bladder. Menstrual periods began at 13 and have been entirely regular until menopause at the age of 48. She has never passed kidney stones or suffered from dysuria. She was always fond of sweets and has used

large quantities of pastry, candy and ice cream. She has never been a lover of protein foods, and at no time in her life has she eaten meats or eggs to any extent. As a girl she was very slender and weighed 125 lb. until 15 years ago, when she gradually increased in weight to a maximum of 164 lb., which is the present weight.

Present illness: Five years ago she noticed that on exertion she became short of breath and had a feeling of fullness over the precordium, hot flushes over the face and neck, and a clutching sensation in the throat. For a month previous she had noticed that the ankles were slightly puffy on retiring at night, but in the morning there was no evidence of swelling. She has had pains in the neck and shoulders, with numbness and tingling of the fingers for the past 2 years. Her family physician found her systolic blood pressure over 250. Numerous readings made over a period of two weeks showed pressures fluctuating from 220 to 250. She was given a low protein diet and large doses of nitroglycerine, and within a month her pressure ranged from 200 to 225 systolic. She was also told to abstain from coffee, and her daily activities were restricted considerably. She suffered from time to time with pain in the epigastrium and slight attacks of pain resembling gallstone colic. During such attacks the pressures showed little increase over the usual readings, namely, 200 to 225 systolic. The advisability of operation for gallstone was considered, but was delayed on account of the hypertension. Three years ago, after a prolonged rest in Florida, pressures decreased temporarily, ranging from 150 to 180. Swelling of the feet has been fairly constant, but at no time has it been sufficiently great to require bed rest. During the past two years she has suffered from insomnia, rarely sleeping more than two or three hours at a time. Fatigue, weakness and irritability have been constant. One year ago she noticed specks floating before the eyes. At first she was inclined to disregard the condition, but later on it interfered with reading. She consulted an oculist, who diagnosed retinitis. The glasses were changed at the time, with only little benefit. Palpitation, oppression over the heart, and clutching in the throat have been present on exertion and have been a source of worry and mental anxiety. There has been no nocturia or dysuria. For the past four years albumin and casts have been present in the urine.

Physical examination: Patient is a fairly well developed adult female inclined to be obese. The skin is soft and has a peculiar yellow gray tinge, but there is no real jaundice. Eyes react normally to light and accommodation. Ophthalmoscopic examination shows the disc outlines somewhat cloudy and the whole of the retina quite pale. Arteries are small and very slightly tortuous. There are no hemorrhages and no exudate on the retinae. Maculae are normal. Ears are normal. Teeth in good condition. Percussion note over the whole chest is resonant and normal. A few coarse musical rales over the whole chest. Occasionally she coughs very slightly and expectorates a very small amount of white purulent tenacious sputum. There is a systolic murmur over the aortic area. Heart slightly enlarged to the left, P. M. I. being 1 cm. outside the MC line. Increase in deep and

superficial areas of cardiac dullness. Intermittent extra systoles. No murmur over the apex. Blood pressure 200/108. Abdomen: moderate tenderness below the right costal margin and extending to the midline with rigidity on deep palpation. The liver edge can be palpated about 1 cm. below the costal margin; the edge is rounded and not tender. Reflexes present. Very slight pitting edema of the ankles. Height 5 feet, 5 inches. Weight 147 lb.

Progress in the Institute: Following admission on March 5, 1922, the patient was given a normal diet with the exception of sodium chloride. The amount of protein was increased over that which she was in the habit of using, and she was persuaded to eat meats, eggs, fish and chicken in normal quantities. Blood pressure was 200/108, and she was slightly dyspneic on climbing the stairs. Throughout her stay in the Institute she improved clinically, dyspnea was less evident on exertion, and she had no attacks of clutching in the throat or precordial distress, although the blood pressures showed only partial improvement, averaging 180/104. The diet was carefully regulated in order to exclude salt, and after five days in the Institute the 24-hour output dropped to less than 1 gm. per day. After a week's treatment, edema of the ankles disappeared entirely and did not return. There was a slight increase in plasma chlorides from 581 mg. per 100 cc. on admission to 593 mg. per 100 cc. on discharge. The blood urea figures were normal, ranging from 20 to 32 mg. per 100 cc. On account of the slow fall in blood pressure, the attempt was made to lower it by more closely restricting the salt in the diet, by parboiling or otherwise reducing the salt of foods. Although the 24-hour chloride output was reduced as low as 0.2 gm., the blood pressures, especially the diastolic, showed little remission. The patient was discharged on March 19 and was instructed to follow a rigidly salt-free diet for an indefinite period.

Progress after discharge: She returned for an office call on April 21, 1922. The 24-hour urine specimen which she submitted showed a total chloride content of 0.63 gm. She stated that she had felt greatly improved and had had no return of the old symptoms. Blood pressure taken after climbing a flight of stairs was 180/104.

This patient has remained faithful to diet up to the present time, taking all precautions to exclude salt. Her physician reported steady fall in blood pressures at each reading. For the past five months the pressures have been as low as 130/85, with a general average of about 140 systolic, with diastolic pressures ranging from 85 to 95. She has had no complaints. Protein in the diet has been that of a normal individual.

Two weeks ago she experienced a third attack of gallstone colic, and upon the advice of her physician, cholecystectomy was performed under ether anesthesia. Eight large stones were found in the gallbladder. She recuperated rapidly. Since operation the pressures have continued low, and the reading made by the family physician ten days ago was 130/80, and examination of the urine was negative for albumin and casts.

There are two noteworthy features of the case; first, the stubborn character at first, so that normal blood pressure was reached only some time after discharge from the Institute; second, the comparatively slight influence of infection, the gall-bladder attacks not being attended with elevations of pressure, and the pressure being completely relieved by diet before the gall-bladder was removed.

Case No. 1080

DATE 1922	URINE				BLOOD			Blood Pressure	
	Volume cc.	Sp. Gr.	NaCl %	Total NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100 cc.	A. M.	P. M.
March 5								200/108	
" 6	1700		.342	6.81	136				
" 7	1500		.056	.840	136	581	32	200/100	188/100
" 8	1100		.132	1.45					222/112
" 9	2000	1009	.082	1.64	142	589	20	188/104	178/108
" 10	1800	1010	.066	1.18				182/110	180/110
" 11	1000	1011	.062	.620				180/112	178/110
" 12	1300	1009	.043	.559				182/112	186/108
" 13	1200	1010	.049	.588	126	593	20	182/110	188/96
" 14	1300	1009	.056	.728				192/130	166/104
" 15	1000		.070	.700					174/108
" 16	1000		.041	.471	116	593	24	196/114	198/118
" 17	1100		.029	.314				170/118	150/108
" 18	1000	1009	.024	.240				162/104	
" 19	900	1008	.024	.216	132				180/116

11. *Eclampsia.*

A unified view of eclampsia has been held by the French school, who consider the condition as the same whether occurring in the puerperal state or in ordinary renal-vascular disease. An important forward step is represented in the adoption of this view by the leading German authority, Volhard. The comparative lack of demonstrable organic lesions is no obstacle to this theory, for a fully comparable picture of albuminuria, slight edema, hypertension, and minimal anatomic changes is typical of some of the early acute nephritides, notably that resulting from scarlet fever. Obstetricians have mostly wasted their efforts in a search for non-existent specific toxins. Toxins, irrespective whether derived from the placenta or from microorganisms, serve only as the cause of the primary vascular injury and of some indefinite constitutional symptoms. The characteristic eclamptic symptoms, ranging all the way from headache to convulsions, are almost certainly due, as shown by Volhard, to secondary consequences of the vascular injury in the form of edema and impaired cir-

culation in the central nervous system. There is no evidence whatever that they are due to any known or unknown products of protein metabolism, or that protein restriction is a rational therapeutic measure in cases uncomplicated by nitrogen retention. This unitarian doctrine, which classes "puerperal eclampsia" as merely a pregnancy nephritis, and establishes a broader definition of eclampsia as a condition resulting from certain renal-vascular injuries in pregnant and non-pregnant patients alike, suggests a trial of salt-free diet also for the puerperal abnormality. We have tried to obtain the aid of several obstetricians in carrying out such a research, but the clinical material is not easily obtainable. Only indifferent results were obtained in a single case, for which we are indebted to the courteous cooperation of Dr. H. B. Kessler of Newark.

Case No. E-1. Female. American. Age. 25. Married. Seen at Newark Maternity Hospital January 28, 1922.

Complaint: Pregnancy, dizziness, headache.

Family history: Irrelevant.

Past history: Always in good condition and never sick in her life with the exception of the usual childhood diseases. She has never suffered from headaches, nausea, vomiting, nocturia or edema.

Present illness: Patient is a primipara, in the sixth month of pregnancy. Since the onset of pregnancy she had made numerous visits to the pre-natal clinic of the Newark Maternity Hospital. Blood pressure readings were made at each visit and found normal and the urine entirely negative for albumin and casts until January 28, when blood pressure of 186/110 was noted. The urine contained a trace of albumin for the first time. She had no complaints, but on close questioning it was found that she had been slightly dizzy and had slight morning headaches for about a week. She was requested to return to the clinic on January 31. Upon this visit the blood pressure was 180/98 and the urine contained 3 plus albumin with numerous casts. She still insisted that she felt well, but on February 1 she was admitted to the Newark Maternity Hospital for observation.

Physical examination: Fairly well nourished woman, small stature, slightly anemic. No cyanosis of the lips and no edema. The eyes react normally to light and accommodation. Fundus examination normal. Ears, nose and throat normal. Lungs normal. Heart normal in size. No murmur at the apex. Aortic second not accentuated. Height 5 ft. 2 in; weight 118 lb.

Progress in the hospital: The patient was put to bed with a view to performing abortion immediately, but it was decided to treat her by close salt restriction. The urine specimen examined on the day of admission showed 3 plus albumin, numerous casts, specific gravity 1016, chloride 0.201%. 6.3 gm. sodium chloride was excreted during the first 24 hours. Blood specimen secured on admission showed blood

urea 72, plasma chloride 593, and plasma sugar 98 mg. per 100 cc. Blood pressure readings taken at 9 o'clock each morning were as follows: first day 176/110, second day 176/110, third day 170/110. The following table gives a summary of the laboratory findings during her treatment:

Case No. E-1

Date 1922	Blood urea mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Plasma sugar mg. per 100 cc.	Urine Na'l %	Urine Alb.	Casts	Blood Pressure mm.	REMARKS
Feb.								
2	72	593	98	.201	+ + +	+ + +	176/110	Ordinary diet.
7	77	593	111	.037	+ + +	+ + +	172/112	On salt-free diet.
14	81	566	107	.032	+ + +	+ + +	166/104	On salt-free diet.
21	65	555	—	.037	+ + +	+ + +	170/95	On salt-free diet. Discharged.
Mch.								
14	66	563	126	.042	+ + +	+ + +	160/96	At home on salt-free diet.
Apr.								
1	62	566	122	.040	+ + +	+ + +	155/90	At home on salt-free diet.

The patient was discharged February 21 and instructed to follow a salt-free diet at home, which she did faithfully and conscientiously. She experienced no symptoms of eclampsia or toxemia. She insisted that she felt well and was eager to carry out pregnancy to term. On her return office calls the pressures were found moderately elevated but she still experienced no symptoms. On April 14 she was readmitted to the hospital on account of nausea and headache. The day previous she had had slight vaginal show and experienced a few pains in the lower part of the pelvis. Abortion was evident. She was given bed rest and small doses of morphine. On April 15 spontaneous abortion occurred.

In the following case there was no opportunity for treatment before abortion, but the observations shown were obtained through the courtesy of Dr. Kessler.

Case No. E-2. Female. American. Age 32. Married. Housewife. Admitted to Newark City Hospital February 26, 1922.

Complaint: Convulsions.

Family history: Irrelevant.

Past history: Was always in good health and suffered no serious illnesses. Married 6 years. One child living and well. Has never had previous miscarriage or abortion. Has never had headache, nausea or vomiting. Appetite normal. No gallstones or appendicitis. Has never had edema of the ankles, shortness of breath, cardiac pain or nocturia.

Present illness: Patient is in eighth month of pregnancy. Two weeks

previous to admission she developed edema of the ankles, which has persisted up to the present time. She had a few frontal headaches which were very mild and which she attributed to constipation. With the onset of edema she noticed slight shortness of breath on exertion. Had no precordial pain or palpitation. Had nocturia for the past two months. Never had hematuria. Yesterday she felt drowsy and weak and suffered from headache the greater part of the day. About 10 A. M. she became nauseated and lost appetite entirely. At 12 noon she had a small vaginal discharge of bright red blood. Labor pains began about 1:30, and at 6 P. M. membranes ruptured but abortion did not occur. At 2 o'clock this morning the labor pains increased in frequency and severity and appeared at two to five minute intervals, lasting for one minute. At 6 A. M. she suddenly had a convulsion followed by unconsciousness. She was admitted to the hospital at 7:30 A. M. A second convulsion followed immediately. She vomited for the first time at 8 A. M. Abortion was performed immediately. The following table gives a record of the chemical findings:

Case No. E-2

DATE 1922	BLOOD			URINE				REMARKS
	Blood Urea mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Plasma Sugar mg. per 100 cc.	Vol. cc.	NaCl %	Total NaCl gm.	Albumin gm. per liter	
Feb. 27	39	560	91	1600	.136	2.17	1.25	General diet.
" 28	34	597	87	2010	.363	9.25	1.25	" "
Mar. 1	25	610	83	1050	.647	6.82	1.25	" "
" 2				1290	.305	3.92	1.50	Salt-free diet.
" 3				1290	.243	2.64	1.25	" "
" 4				630	.235	1.48	1.75	" "
" 5				800	.140	1.16	2.00	" "
" 6				960	.066	.63	1.00	" "
" 7				810	.033	.26	1.00	" "
" 8	15	581	74	890	.012	.10	1.00	" "
" 9				1095	.058	.62	75	" "
" 10	16	552	83	1080	.062	.64	.50	Discharged.

A blood specimen taken February 27, the day following abortion, showed blood urea 39, plasma chloride 560, and plasma sugar 91 mg. per 100 cc. The urine contained 1.25 gm. albumin per liter. A second blood analysis taken the day following showed blood urea 34, plasma chloride 597, and sugar 87 mg. per 100 cc.

During the first three days of hospital treatment her diet was ordinary light diet as given in a general hospital. On March 2 a special salt-free diet was given, on which edema disappeared within 48 hours. There was a prompt fall in the urine chloride percentage and total 24-hour chloride, as shown in the table. She was discharged March 10 in good condition.

The only feature of interest is the apparent chloride retention at the time of the eclamptic attacks, indicated by edema, the elevation of plasma chloride occurring only later.

The fact is familiar that the French school have long used salt restriction for the treatment of puerperal eclampsia. Their success has not been sufficient to convince most physicians in other countries. The difficulty may be partly explained by the undue laxity of salt privation heretofore, but also is largely inherent in the French conception of the condition as a simple salt retention, which must clear up on withdrawal of salt. This entire viewpoint in now known to be erroneous, in so far as it takes notice only of the kidneys and their supposed threshold, and ignores general capillary permeability and the equilibrium between blood and tissues. This factor is clearly seen in scarlatina, in which the toxic vascular injury is directly responsible for both edema and hypertension, and, as salt plays only a minor secondary role, salt restriction may be somewhat beneficial but will often fail to produce any important change in either the edema or the hypertension. The conditions in the average pregnancy case are not like those of chronic vascular or renal sclerosis, in which hypertension is maintained by the organic changes resulting from causes which long ago ceased to operate; but rather they are those of acute or subacute nephritis, in which injury from toxic agents is actively in progress and structural changes are still slight. Accordingly, the most powerful aid in a nephritis which is caused by infection is afforded by recovery from the infection, and in a nephritis which results from pregnancy is afforded by termination of the pregnancy. It is not to be expected that the mere sparing of a damaged function by diet will give results in the presence of an active toxic process equal to those obtained in the absence of such a process. On the other hand, the complete or partial failure of salt-free diet to relieve hypertension under such conditions speaks no more against its general effectiveness for this purpose than the failure to clear up edema under the same conditions supports any general argument against salt-free diets for edema. Furthermore, authorities with practically no dissent are convinced of the benefit of diet treatment for puerperal eclampsia, and few obstetricians would willingly abandon such procedures, particularly in the form of milk diet, for treat-

ment or prophylaxis. Accordingly, it remains only to determine accurately the particular feature of the diet which gives benefit; whether with milk diet, for example, it results from the general undernutrition, or the low protein, or the reduced salt intake or the comparatively abundant fluid intake. These points are perfectly feasible to test, and the information should afford a basis for a better dietetic treatment. For example, if the analogy can be maintained with other states of hypertension, in which sodium chloride is always the essential injurious agent in the diet, while excessive fluid intake is also injurious in some cases, but protein and undernutrition are unimportant, it becomes a simple matter to prescribe diets for puerperal eclampsia which are lower than milk in chlorides and water and at the sime time provide more adequately the protein and calories which the pregnant woman needs. Laboratory studies of the chloride metabolism may also assist in the early diagnosis and prophylaxis of eclampsia, provided the investigator does not fall into the error of ignoring the variable equilibrium between blood and tissues and the primary role played by abnormalities of vascular permeability.

12. *Retinitis.*

Retinal changes are of the utmost importance practically, as responsible for the distress of blindness and as proof of a severe and dangerous general condition, and also theoretically, as related in all probability to similar phenomena in the kidneys, in the central nervous system, and in the body at large, and as affording a valuable means of studying these phenomena. Attemps were therefore made to cooperate with competent oculists not only with regard to the retinal lesions encountered incidentally in this series of hypertension cases, but also in the study of the greatest possible number of retinitis cases of all kinds, with or without hypertension or known nephritis. The following two cases are illustrative.

Case No. 604. Male. Hebrew. Age 21. Married. Salesman. Admitted May 14, 1921.

Complaint: Partial blindness of the right eye fifteen months ago. Blindness in the left eye three weeks ago. Dyspnea on exertion.

Family history: Mother died at 48 of Bright's disease. Otherwise negative.

Past history: Always strong and healthy, but with a tendency to obesity since the age of 23, when his weight suddenly increased from

150 lb. to 182 lb. Has never used alcohol, but has used large quantities of salt. Has noticed some dyspnea on exertion, but at no time had cardiac pain or palpitation. Fifteen years ago he had an attack of nephrolithiasis, which was very painful and required two weeks' stay in bed. Classical symptoms were present.

Present illness: On January 3, 1920, sudden complete blindness of the right eye occurred. He had no previous symptoms with the exception of slightly hazy vision in the same eye for two or three days, which he had disregarded. The left eye was not involved at this time. Eye-grounds were examined thoroughly by an occulist, who told him there was considerable swelling in the right eye, and that the left showed slight similar changes. The blood pressure was found to be 160 to 170 systolic. For three years he was almost totally blind in the right eye, except for light perception; then there was some slight improvement, but at no time since has the vision returned sufficiently for him to recognize persons across the street. Numerous blood pressure readings were made since the onset. During the first six months the systolic pressure ranged from 160 to 170. There has since been a steady rise to constant readings of 200 mm. He has noticed gradual loss of visual acuity of the left eye for the past seven months, but was able to read until three months ago. Examination of the eye-grounds was made by his oculist a week ago, with the following report: Right eye: the optic nerve has a whitish paleness; marked tortuosity of the retinal vessels, particularly the arteries. The vessels are smaller than normal, and indistinct in places. There are chorioretinal changes at the macula. Vision 20/40. Left eye: optic disc is pale, and shows definite papillitis. Marked tortuosity of the retinal vessels. Retinal veins are distended, one small hemorrhage seen; vision 20/40. There has been no complaint of headaches, palpitation, pain, edema, etc., and the patient has continued to feel well except for the eye trouble and slight dyspnea on exertion. No benefit was obtained from treatment prescribed for him at the Rockefeller Institute Hospital, namely "abstinence from meat and from overeating, very limited use of salt, and cessation of work daily at the time of the evening meal".

Physical examination: Well developed, moderately obese male, in no acute distress, but with slight dyspnea after climbing stairs. The gait is steady, but on account of impaired vision he is careful in walking. His main complaint is his eye condition. Head: scalp, ears, and nose normal. Teeth are in poor condition with numerous fillings. Tongue protrudes in the midline without tremor. Eyes: slight exophthalmos; pupils are equal and react to light and accommodation; intraocular tension normal in both eyes. Ophthalmic examination: Right eye: the disc has lost much of its color and the outline is hazy, but still distinct. The retina has increased color. The arteries are small and indistinct in places, and tortuous. Arteries are shorter than normal. No hemorrhages seen. Choroiditis at the macular area. Left eye: disc indistinct, vessels similar to those of the right eye. One small hemorrhage seen. Heart: diffuse precordial bulging over the

whole apex region. P. M. I. and apex beat cannot be made out distinctly. On percussion the left costal border extends 2½ cm. outside MC line. Deep and superficial cardiac dullness is increased. There is no pulsation in the episternal notch. Radial vessels are thickened and definitely palpable. Heart rate about 70; aortic second sound is increased. No murmurs over aortic region or at the apex. The urine contained traces of albumin and no casts. Height 5 ft. 7 in. Weight 154 lb.

Progress in the Institute: Treatment consisted of a strictly salt-free diet of 75 gm. protein, 70 gm. carbohydrate and 1400 calories. On account of the tendency to obesity, a glucose tolerance test was performed. 100 gm. glucose given by mouth produced marked hyperglycemia and 0.5 per cent. glucose in the urine at the end of the first and second hours. There was some change in the blood pressure readings during the first week, and the general average during the hospital stay was much lower than those taken by his family physician previous to admission. On the fifth day after admission, patient noted an improvement in his vision, namely ability to identify smaller letters than formerly. He also noticed that objects appeared less hazy, and general visual acuity improved. This encouraged him to follow the diet prescribed. He was also markedly relieved of dyspnea.

Progress after discharge: Patient was discharged on May 27, 1921, and advised to take a rigidly salt-free diet, with restricted starches and sugars. He returned for an office call on June 16. He had adhered closely to the salt-free diet, as shown by a 24-hour urine specimen of 1000 cc., with chloride percentage of 0.07 per cent, making a total chloride excretion of 0.7 gm. His blood pressure taken immediately after coming to the office was 150/96. Blood analysis was: plasma chloride 552, plasma sugar 115, blood urea 14 mg. per 100 cc. During the interval which had elapsed since discharge, he had noted a steady slow improvement in visual acuity. He was seen again on July 1, 1921. Vision had become practically stationary. Blood pressure was 128/80. The blood analysis was: plasma chloride 589, plasma sugar 107, blood urea 12 mg. per 100 cc. The 24-hour urine NaCl output was 0.5 gm. On April 29, 1922, he returned for another visit. His physical condition had remained good. There had been no further loss or impairment of vision. He had adhered rigidly to the salt-free diet prescribed, with the exception of two weeks in February, 1922, when on account of business affairs he was unable to obtain a proper one. During this time his blood pressure was found elevated by his family physician. He then noted changes in his vision; objects became blurred and hazy, and he was unable to identify small objects and letters as readily as he formerly did. He immediately returned to the rigid diet, and noticed an improvement in his vision. A blood analysis showed plasma chloride 581, plasma sugar 122, blood urea 12 mg. per 100 cc. Twenty-four-hour urine specimen, volume of which was 900 cc., contained 0.070 per cent. NaCl.

Case No. 604

DATE 1921	NaCl in diet gm.	URINE				BLOOD			Blood Pressure A. M.
		Volume cc.	Sp. Gr.	NaCl %	NaCl gm.	Plasma Sugar mg. per 100 cc.	Plasma NaCl mg. per 100 cc.	Blood Urea mg. per 100cc.	
May 13	0					090	612	24	
" 14	0	650	1.020	.52	3.40				210/137
" 15	0	750	1.022	.42	3.21	111	608	28	
" 16	0	750	1.022	.30	2.29				204/130
" 17	0	420	1.024	.111	.46				
" 18	0	505	1.022	.22	1.13				
" 19	0	550	1.022	.24	1.36				166/93
" 20	0	700	1.022	.04	.28				
" 21	0	675	1.022	.04	.29				175/105
" 22	0	600	1.026	.16	.96				
" 23	0	600	1.024	.16	.98				
" 24	0	550	1.024	.20	1.13				
" 25	0								200/128
June 16	0	1000		.07	.70	115	552	14	150/96
July 1	0	1000		.049	.49	107	589	12	128/80
1922									
Feb. 7	0	900		.070	.63	122	581	12	
" 26	0	520	1.024	.19	1.02	122	612	24	

Case No. 349. Male. American. Age 48. Married. Merchant. Admitted October 5, 1920.

Complaint:. "Blurred and cloudy vision", "double vision", "migraine", dyspnea on exertion.

Family history: Negative.

Past history: Usual childhood diseases. Severe attack of typhoid fever at 21, with relapse. Always had tendency to be overweight, and never made a serious attempt to reduce by restricting diet. He habitually used excessive salt. Five years ago he had considerable pain and tenderness over the gall-bladder region, and similar attacks have occurred on several occasions since.

Present illness: Four years ago patient had an attack of dizziness and disturbance of vision. He noticed that all objects were cloudy and hazy and he became unable to recognize a person across the street. Headache was also present. The day after the onset his physician found the pressure 190 systolic. He was put on a diet omitting red meat, coffee, tobacco, alcohol and condiments. He was also advised to reduce his body weight, which he did, the weight dropping from 200 lb. to 180 lb. The pressure remained the same, namely 190 systolic, for three years and nine months, when he had another attack of dizziness, headache, and impaired vision of greater degree than on the first occasion. Within 24 hours his visual field became narrower and double vision occurred. The condition was temporary, subsiding within a week. The pressure was found to be 200 systolic. Dyspnea on exertion was noted at this time, but caused little annoyance except

after unusual exertion. Attacks of migraine became frequent and failed to improve under medication of various kinds. His chief complaint on admission was blurred vision and headache.

Physical examination: Well developed, active adult male. Height 5 feet 11 inches, weight 175 lb. Pupils react to light and accommodation and are of equal size. Slight exophthalmos. The retinae are hazy and rather pale, and the vessels sclerotic. With the exception of a few cholesterol deposits, the fundi are otherwise negative. The patient is able to read only the headlines of the newspapers, and complains that he is unable to recognize his friends at a distance of more than about 40 feet. Ears and nose negative. Tonsils are large. Lungs normal. The heart is enlarged 3 cm. beyond MC line. There are no thrills or murmurs. Aortic second sound accentuated. Blood pressure 208/100. Radial, temporal and brachial vessels are thickened. There is no dyspnea, cyanosis or edema. Abdomen negative throughout. Muscular and nervous systems normal.

Progress in the Institute:. A salt-free diet without limitation of protein or calories was prescribed. Within three days an improvement in vision permitted reading with greater ease, and the blur and haze which had surrounded the letters had disappeared. On the fourth day after admission the dull frontal headaches lessened, and disappeared entirely within the following few days. He was discharged free from complaint October 12, to return to his home in the South.

Progress after discharge: On July 7, 1921, he returned for an office call. He had adhered as faithfully as possible to the diet, but occasionally had eaten salt on trips away from home. Headaches remained absent, and his vision remained good. Blood pressure 160/90. He was again seen on March 13, 1922. Except for an occasional sensation of constriction about the head, he felt well. He had no dyspnea or headache, and did not complain about his vision. The condition is said to be the same at the present time.

It may be conceded that an active infectious process may sometimes bear the same relation to retinitis as to other vascular disorders, so that other treatment is nullified and only removal of the source of intoxication may arrest the process. On the other hand, it is an easily demostrable fact that dietetic control of the blood sugar in diabetes definitely halts diabetic retinitis. The possibility of a chemical exciting cause and an effective dietetic treatment of retinitis is thus demonstrated. We are not in position to make broad assertions, but our limited experience to date suggests that sodium chloride is the most important dietary factor in the retinitis of renal and vascular disorders with or without hypertension, and probably also in many of the so-called "idiopathic" forms of retinitis. The obvious comparison with vascular crises, angina pectoris, apoplexy, etc., and the essentially vascular

nature of retinitis, with its hemorrhages, infiltration and edema, lend theoretical support to this view. Without denying that products of protein metabolism may sometimes play some part, it may still be said that the appearance or disappearance of retinal lesions in consequence of increase or decrease of protein feeding or of nitrogen retention has never been demonstrated, and the burden of proof rests upon those who believe in such a toxic role of protein products. Opposed to the fruitless search for mysterious toxins is our experience of definite checking of retinitis and of related vascular processes in other parts of the body by salt-free diet. When the general results of the treatment are successful, the retinal complication seems likewise to be cleared up in a lasting manner so that it does not progress further. Such observations, if confirmed, not only establish salt restriction as the best practical treatment for retinitis, but also have theoretical applications which are too lengthy to discuss here. We believe this investigation should be continued, and as we are not qualified for the necessary retinal examinations and judgments, and as few ophthalmologists are equipped to manage accurate salt-free diets, simple as these may appear, we still desire opportunities for the cooperative study of cases of this type.

Summary and Conclusions

1. This paper describes 180 severe cases of hypertension treated by close restriction of the sodium chloride intake, for periods from one month to three years. Fully normal blood pressure was restored in only 34 cases (18.9 per cent.). In 75 other cases (41.9 per cent.) the relief of hypertension and other symptoms was sufficient to be regarded as a distinct therapeutic success. Transitory benefit, followed by relapse or death after several months, was obtained in 16 cases (8.9 per cent.). Complete failure of treatment was encountered in 55 cases (30.5 per cent.) The total mortality for the four year period was 25 (13.8 per cent.), with no appreciable difference between cases of long and short duration, as success or failure is determined by the character of the case rather than by a time element. Incomplete and unsuccessful results are be-

lieved to be due to organic changes which cannot be removed by a treatment based only on the principle of functional rest. In successful cases not only are symptoms relieved but the progressiveness is arrested, so far as the present duration of observations can decide.

2. The series has been divided for convenience into four groups, namely: A. 73 cases with initial plasma chloride concentration above 580 mg. per 100 cc.; B. 31 cases with initial plasma chloride concentration below 580 mg. per 100 cc.; C. 33 cases associated with nephritis, as determined chiefly by impaired excretion of nitrogenous substances; D. 43 cases complicated by diabetes. This classification is purely empirical, and in large measure must be arbitrary and inexact; but it has seemed to have some prognostic value and may therefore indicate some real difference between cases. On the whole, the "pure" hypertension cases with high plasma chloride carry a better prognosis than those with low plasma chloride, perhaps because the pressure in the former group is governed more by a functional element of chloride retention and in the latter group more by strictly organic changes. The nephritic group, as above defined, shows by far the highest proportion of failures and deaths. The complication with diabetes does not detract from the prognosis or treatment. Though hopeless cases are sometimes encountered in this group, the outlook as regards hypertension seems in general somewhat better by reason of the diabetes, as the sugar seems to play a part somewhat like salt, and reduction of the hyperglycemia may sometimes suffice to reduce the blood pressure or may supplement the influence of salt restriction.

3. The chief requirement for success, which needs emphasis above everything else in the use of this treatment, is that sufficiently strict salt privation must be carried out for a sufficient length of time. In relatively mild cases, pressures which are sometimes very high may be reduced within a short time by comparatively lax diets which furnish several grams of sodium chloride daily. One proof of the severity of the cases composing this series is that the sodium chloride tolerance was very seldom above 2 grams, and in 112 of the 180 cases the best results could be obtained and maintained only by diets which kept the sodium chloride excretion below 0.5 gm. in each 24 hours. Institutional care is generally advisable for the

study of such cases and the training of the patients in diets which shall be sufficiently salt-free and at the same time adequate and appetizing. As symptoms of weakness and anorexia appear in some patients after several days to several weeks of salt privation, it is necessary to determine precisely the salt tolerance in each individual case so as to insure freedom from privation symptoms on the one hand and the best control of the hypertension on the other. This complete result has generally been attained in from two to four weeks prior to discharge, but some cases which showed little if any initial benefit gradually improved through several months to a year of strictest diet at home, so that in every instance persistent effort is necessary before failure is admitted. Though the treatment reduces the plasma chloride concentration in most cases and the renal chloride threshold in many cases, it is of theoretical interest that neither the blood pressure level nor the occurrence of privation symptoms bears any fixed relation to these factors, the general vascular permeability and equilibrium between blood, tissue fluids and cells being obviously a decisive element. Points worth mentioning on the practical side are: first, that reports have no value as evidence on this question unless they are controlled by laboratory analyses covering the entire period of observation, to prove the degree of accuracy of salt privation and exclude the errors of diet which so easily occur; second, the continued fidelity to such strict diets on the part of such a large proportion of patients is one proof of the benefit which they experienced from the treatment.

4. Facts are presented to show that the therapeutic results described are not due to physical or psychic rest, protein restriction, or general undernutrition. We believe that theories of excesses in food or drink, of intoxication by nitrogenous substances, or of either nervous or endocrine disturbances are improbable as regards the actual etiology of hypertension, and our experience coincides with that of the general medical profession in showing that treatment based upon such ideas accomplishes nothing fundamental. There are occasional emergency uses for bed rest, bleeding, and drugs such as digitalis and nitrites. All such measures often fail in cases in which salt restriction succeeds, and we have never seen them accomplish any appreciable benefit in cases in which salt restriction has failed. The use of these measures, or of hydro-

therapy, physicotherapy or the like is to be regarded as the mere treatment of a symptom, which does not alter the fundamental clinical condition, the progressive tendency or the prognosis. The existing mortality rates furnish a sufficient judgment of the prevailing customary methods of treatment.

5. Chloride restriction has acted favorably upon the serious accompaniments of hypertension such as cardiac failure, incipient pulmonary edema, and vascular crises, including to some extent angina pectoris. We believe it to be the best treatment for eclampsia in the broad sense, though in the puerperal form an active toxic process, comparable to that in acute nephritis, may seriously limit the possibilities of any dietetic treatment. With due allowance for other possible causes and treatments, our few observations create the impression that sodium chloride is the most important direct factor in nephritic retinitis, either with or without hypertension, and the arrest of this process by salt privation is highly important practically and theoretically. This entire group of conditions may be viewed broadly as vascular phenomena, the primary damage of vessels having originated from infectious or toxic causes often temporary in character, and the resulting abnormalities of permeability being responsible for the secondary clinical and pathological processes in the form of edema, hemorrhage, etc., in various organs. It appears rational that sodium chloride, as the principal osmotic regulator of the body, should play an important part in such phenomena. Clinical experience supports the view that chloride restriction acts powerfully not only in relieving immediate symptoms but also in checking the progressiveness of the condition.

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TABLE A.

Cases of hypertension with plasma chlorides above 580 mg. per 100 cc.

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case		Symptoms	Height cm.	Body Weight kg.			LABORATORY FINDINGS							BLOOD PRESSURE				Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
					Before Adm. Yrs.	After Adm. Mos.			Std. Normal	Before Adm.	Final	Plasma NaCl mg. per 100cc.		Blood Urea mg. per 100cc.		Other Tests at Admission			Before Treatment		After Treatment				
												Initial	Final	Initial	Final	Albumin	Casts	Plasma Sugar mg. per 100cc	Systolic	Diastolic	Systolic	Diastolic			
4	F	80	Aug., 1919	Rest	10	40	Dizziness Weakness	165	63	56	56	610	580	24	30	+	+	130	220	130	170	95	3 mos.	0	Improved.
53	F	63	Sept. 22, 1919	Rest Drugs	8	48	Vertigo Headaches Palpitation Blurred vision	165	63	64	64	638	600	21	25	+	+	115	225	90	166	78	1 mo.	0	Salt-free diet. Improved.
63	F	59	Sept. 26, 1919	Low protein Purgatives	4	39	Fatigue Amnesia Palpitation Dyspnea Amaurosis	160	63	59	59	616	585	20	24	—	—	134	240	110	168	90	2 mos.	0	Patient well. Pressures average about 160 to 180 systolic. Two relapses due to laxities in diet. Phthalein 64%. Readmitted. Condition improved.
102	M	56	Dec. 1, 1919	Colon irrigations Low diet	5	36	Depression Insomnia	175	76	....	....	610	580	30	28	—	—	.....	220	140	190	120	.....	0	Improved.
183	M	51	March 12, 1920	Red meats restricted Alcohol restricted	10 mo.	33	Headaches Irritable	178	78	75	75	598	605	24	22	+	+	123	208	116	170	105	4 mos.	3	Pressures previous to admission ranged from 200 to 250 systolic. Headaches disappeared.
188	M	35	March 15, 1920	Low protein Rest Purgatives	6	33	Precordial oppression Nervousness Fatigue Irritability	175	72	72	72	593	538	30	18	+	+	97	214	100	126	62	2 yrs.	0	Patient well. Follows strictly salt-free diet. Readmitted Oct. 14, 1922, with normal pressures and without albumin or casts.
197	M	46	March 25, 1920	Low protein Potassium iodide	2	33	Headaches Vertigo Dyspnea	173	73	82	82	615	590	18	....	—	—	177	230	110	158	95	2 wks.	2	Dyspnea, vertigo and headaches disappeared.
224	M	64	April 12, 1920	Colon irrigations Digitalis Low protein Teeth extracted	7	32	Dyspnea Palpitation Blindness	170	74	50	50	598	580	34	12	+	+	96	192	90	200	100	3 mos.	0	Unimproved. Chronic myocarditis. Mitral insufficiency. Arteriosclerosis.
240	F	53	April 28, 1920	Thyroid Rest Low protein	1	32	Dizziness Palpitation Tinnitus aurium	170	71	97	96	600	580	22	36	+	—	128	186	120	130	80	1 wk.	0	Complicated by obesity. Improved.
281	F	53	June 15, 1920	Sodium nitrite	4	30	Headaches Fatigue Loss of weight Palpitation	175	75	78	79	603	578	12	18	—	—	107	196	110	150	98	2 wks.	0	Greatly relieved. Headaches and palpitation disappeared. Follows salt-free diet.

289	M	49	June 14, 1920	Low protein Restricted salt	2	49	Blurred vision Palpitation Nocturia	178	77	75	73	595	563	22	22	—	—	168	192	100	120	80	1 wk.	2	One year previous improved on salt-free diet under another physician. Follows salt-free diet. Vision improved. Palpitation decreased.
322	F	60	Aug. 20, 1920	Low protein Amyl nitrite	2	28	Precordial pain Headaches Angina pectoris Dizziness	165	63	70	67	593	570	37	16	+	—	111	185	100	145	80	6 mos.	0	Partial improvement.
349	M	48	Oct. 5, 1920	No red meats No stimulants Rest	4	27	Impairment of vision Palpitation Fatigue	180	80	79	79	580	580	45	36	+	—	105	211	124	157	100	2 das.	2	Marked improvement in vision. Follows salt-free diet. Pressures low. Has gained weight past year.
364	F	61	Nov. 4, 1920	No red meats Rest Potassium iodide	6	26	Occipital headaches Paresthesia Palpitation	163	64	64	62	581	581	24	. .	—	—	161	218	100	182	100	1 mo.	2	Paresthesia continues. Palpitation relieved.
378	M	50	Dec. 11, 1920	Low protein Rest		24	Headaches Paresthesia Nocturia	170	70	67	59	608	618	26	28	—	—	102	220	140	160	104	1 wk.	1	Headaches disappeared. Improved.
400	F	47	Dec. 30, 1920	Low protein Purgatives Teeth extracted	2	24	Headaches Dizziness Nocturia	.....	..	59	59	635	564	44	40	—	—	.....	198	100	172	100	2 mos.	0	No improvement.
405	M	40	Nov. 19, 1920	No red meats No stimulants No tobacco	1	25	Headaches	158	61	75	73	620	590	25	25	—	—	....	190	100	145	80	1 mo.	0	Immediate relief from headaches. Improved.
419	F	48	Jan. 12, 1921	Low protein	1	24	Dizziness Headaches	175	74	101	77	622	601	22	32	+	+	137	212	100	152	70	4 das.	0	Excellent result.
421	F	52	March 8, 1921	Low protein Digitalis	2	22	Fatigue Paresthesia	170	71	75	73	618	581	26	28	—	—	98	188	110	130	80	2 mos.	2	Improved. Strength increased. Follows salt-free diet.
429	F	51	Feb. 4, 1921	Protein-free diet Rest	4	23	Precordial pain Dyspnea Dizziness Headaches	165	67	63	59	608	571	27	34	—	—	112	236	108	182	102	1 yr.	0	Marked improvement with relief of symptoms.
449	M	45	Feb. 9, 1921	Rest No tobacco Low protein	5	23	Paresthesia Palpitation Dyspnea	170	70	68	67	585	589	42	42	—	—	127	225	140	197	138	1 mo.	0	Headaches disappeared. Symptomatically relieved. Patient follows strict diet.
501	F	57	Feb. 28, 1921	Low protein	2	22	Flushes Palpitation Neuritis	170	72	61	61	610	593	26	24	—	—	113	184	104	146	80	1 wk.	1	Symptomatically improved. Follows strictly salt-free diet.
506	M	57	March 6, 1921	No meats Purgatives Hydrotherapy Tonsillectomy Teeth extracted	1½	22	Dyspnea Palpitation Headaches Fatigue	155	62	58	56	594	589	40	40	+	+	100	208	118	120	60	2 wks.	1	Relieved temporarily. Downward progress

TABLE A. *(Continued).*

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	LABORATORY FINDINGS: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	BLOOD PRESSURE: Before Treatment: Systolic	Before Treatment: Diastolic	After Treatment: Systolic	After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gms. per day	REMARKS
508	M	62	Feb. 28, 1921	Low protein Teeth extracted Hydrotherapy Vegetable diet	5	22	Dyspnea Dizziness Flushes Palpitation	163	61	63	63	589	593	22	30	+	+	131	215	114	210	120	1 yr.	0	Intractable case. No improvement.
546	F	50	May 19, 1921	No meat	8	19	Weakness Dizziness Dyspnea Flushes	173	73	78	76	581	579	18	27	—	—	115	200	114	190	106	1 wk.	2	No improvement. Continued to have flushes.
549	F	54	May 1, 1921	No meats Teeth extracted	5	20	Nocturia Dizziness Amaurosis	173	74	65	63	608	560	38	20	+	+	112	192	101	169	90	1 yr.	0	Improved. Follows salt-free diet.
551	M	53	May 5, 1921	Teeth extracted Undernutrition Low protein	2	20	Epistaxis Headaches Nocturia	173	73	70	69	585	578	26	....	—	—	104	218	120	220	130	3 mos.	0	Symptomatically improved. Follows strictly salt-free diet.
557	M	65	March 5, 1921	Low protein Morphine Potassium iodide Digitalis	12	22	Dyspnea Headaches Angina pectoris	170	71	72	71	612	536	30	32	+	+	104	232	116	206	104	8 mos.	2	Dyspnea diminished. Headaches relieved.
562	M	59	May 27 1921	Low protein Undernutrition Potassium iodide Retirement	1	21	Nocturia Dyspnea Sudden blindness	190	93	121	105	610	570	35	30	+	+	...	204	130	170	90	7 mos.	0	Readmitted June, 1922. Blood pressure 150/80. Resumed law practice 6 months ago. Diet normal except salt.
590	F	63	April 30, 1921	Undernutrition Low protein	1	22	Dyspnea Dizziness Tinnitus aurium	173	70	87	81	589	590	32	37	+	+	113	172	80	170	100	6 wks.	0	Not improved.
604	M	41	May 14, 1921	Rest No meats Low protein	1½	21	Sudden blindness Dyspnea Nocturia	170	70	85	81	608	612	28	24	+	—	111	210	137	185	105	1 yr.	2	Improved. After discharge followed strictly salt-free diet. Pressures ranged from 156/90 to 185/105. Vision improved.
656	M	62	July 19, 1921	Rest Low diet Saline cathartics	1	17	Nocturia Headaches Amnesia Paresthesia Dyspnea Palpitation	182	84	75	76	589	536	22	16	—	—	109	186	120	178	110	8 mos.	0	Follows an accurately weighed diet. No return of vascular crises. Improved.
663	F	50	July 23, 1921	Low protein Rest	1	17	Weakness Dyspnea Flushes	151	60	75	74	585	507	12	20	—	—	111	208	106	156	100	3 mos.	0	Follows salt-free diet. Improved.

674	M	51	July 31, 1921	Electrotherapy Teeth extracted Undernutrition	2	5	Palpitation Precordial distress Impaired vision Headaches Fatigue	170	71	73	71	585	449	16	20	—	—	128	220	140	220	110	5 mos.	0	Advanced case. No improvement. Died December, 1921.
681	M	68	Aug. 29, 1921	Rest No alcohol No tobacco Drugs	4	16	Epigastric distress Nocturia	172	74	64	64	593	581	20	..	—	—	142	176	106	130	70	2 wks.	2	Blood pressures have never exceeded 140/86. Greatly improved. Follows strictly salt free diet. Present weight 64 kg.
722	F	62	June 6, 1921	Epsom salts No protein	4	19	Amaurosis Dyspnea Headaches Fatigue	155	61	76	70	599	560	30	26	+	+	108	192	80	150	100	2 wks.	1	Improved. Headaches disappeared. Return of palpitation with laxities in diet.
751	F	50	July 25, 1921	Colon irrigations	2	17	Flushes Palpitation	.....	....	60	59	585	580	16	18	—	—	106	160	70	128	86	2 wks.	4	Symptomatically improved. Follows careful diet.
779	M	64	July 22, 1921	Digitalis	3	17	Headaches Vertigo Nocturia	163	66	53	56	608	590	54	40	—	—	143	186	120	196	108	3 wks.	0	Unimproved. Careless with diet.
803	F	56	Aug. 15, 1921	Low protein Rest	1½	16	Fatigue Angina	163	66	107	101	601	566	18	28	—	—	107	190	100	160	80	6 mos.	2	Follows strictly salt-free diet at home. Strength improved.
836	M	55	Sept. 9, 1921	Hydrotherapy Electrotherapy	3	15	Palpitation Dizziness Headaches Nocturia	168	70	79	76	594	608	26	26	—	—	139	200	118	160	100	2 wks.	1	Nocturia and headaches disappeared.
890	F	60	Oct. 21, 1921	No meats Undernutrition	5	14	Depression Palpitation Fatigue Dizziness Headaches	159	..	89	80	598	562	30	32	—	—	...	220	110	164	90	3 wks.	1	Improved.
925	F	52	Nov. 5, 1921	Rest	8	13	Neurasthenia Nocturia	168	69	77	73	582	593	20	26	—	—	81	168	120	160	100	1 mo.	0	Practically no change or improvement.
956	F	35	Nov. 7, 1921	Purin-free diet No meats	1	13	Palpitation Dyspnea	165	63	76	68	620	590	22	...	+	+	157	206	120	140	85	8 mos.	2	Improved. Follows careful diet.
958	F	54	Nov. 11, 1921	No meats Digitalis	10	13	Edema Paresthesia Substernal oppression Nocturia Amaurosis	155	61	73	62	601	521	48	40	+	+	159	210	138	158	115	9 mos.	0	Anasarca disappeared. Marked improvement. Follows strictly salt-free diet.
974	F	57	Jan. 11, 1922	Hydrotherapy Electrotherapy Low protein	12	11	Dyspnea Headaches Palpitation	160	64	86	83	610	552	26	22	—	—	132	200	130	150	100	10 das.	2	Follows accurate salt-free diet. No headaches. Less dyspnea.

TABLE A. *(Continued).*

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	LABORATORY FINDINGS: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	BLOOD PRESSURE: Before Treatment: Systolic	BLOOD PRESSURE: Before Treatment: Diastolic	BLOOD PRESSURE: After Treatment: Systolic	BLOOD PRESSURE: After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
999	M	53	Jan. 15, 1922	Low protein Rest	1	11	Fatigue Weakness Paralysis Substernal oppression	173	74	76	70	606	573	42	46	—	—	178	180	100	126	90	2 wks.	2	Follows strictly salt-free diet. Fatigue relieved.
1011	M	54	Dec. 4, 1921	Undernutrition	5	12	Palpitation Nocturia Precordial distress	180	81	68	68	597	560	20	22	—	—	123	172	80	160	90	2 mos.	0	Partial improvement. Follows an accurate diet.
1015	F	49	March 5, 1922	Rest Low protein	5	9	Weakness Palpitation Flushes Hemiplegia	170	71	73	68	597	603	24	32	....	....	131	220	136	166	100	2 mos.	0	Improved.
1023	M	57	Dec. 13, 1921	Undernutrition No red meat	5	12	Headaches Dizziness	168	69	87	86	643	589	48	29	—	—	140	200	100	160	90	1 mo.	2	Observations made while engaged in business.
1029	F	38	Dec. 27, 1921	Drugs	5	12	Palpitation Flushes Headaches Insomnia	173	70	63	60	589	606	32	40	+	+	115	180	130	182	131	3 wks.	0	Not improved. Palpitation continued.
1031	F	46	Dec. 27, 1921	Low protein Rest Hydrotherapy	2	12	Dyspnea Pressure in head	158	62	74	67	606	589	46	24	—	—	143	180	100	156	98	1 yr.	1	Symptomatically improved.
1053	F	64	Jan. 26, 1922	Drugs	5	11	Neuritis	160	64	72	68	606	573	26	30	+	+	156	200	96	150	90	1 mo.	0	No relief. Marked arteriosclerosis. Lost from observation.
1070	F	56	Feb. 13, 1922	Rest	3	10	Palpitation Flushes Dyspnea	155	61	62	60	620	597	22	20	—	—	131	220	130	166	102	6 wks.	0	Symptomatically relieved.
1073	M	50	Feb. 17, 1922	Hydrotherapy Rest	3	10	Dyspnea Fatigue Nocturia	163	65	86	80	593	548	60	56	—	—	145	200	130	192	104	3 wks.	2	Improved. Readmitted December, 1922, blood pressure 180/95. Follows careful diet.
1079	M	60	Feb. 28, 1922	No meats Rest Drugs	1 mo.	10	Nervousness Nocturia	158	63	69	64	585	560	42	18	—	—	133	210	120	150	92	2 wks.	1	Faithful to diet. Dyspnea relieved. Improved.
1080	F	53	March 5, 1922	Low protein Rest	5	9	Flushes Palpitation Edema	165	67	77	71	581	593	32	24	—	—	136	188	100	150	108	3 mos.	0	Faithful to diet. Relieved of fatigue. Symptomatically improved.

1081	F	68	March 5, 1922	Rest Low protein	2 mo.	9	Dyspnea Dizziness Headaches Irritability	158	63	67	64	610	560	29	18	—	—	148	210	110	170	108	3 mos.	0	Faithful to diet. Dyspnea relieved.
1084	F	62	March 9, 1922	Undernutrition Rest	10	9	Headaches Palpitation	155	61	76	70	593	566	15	38	—	—	124	232	134	168	100	5 wks.	0	Symptomatically relieved. Follows salt-free diet.
1150	F	51	May 15, 1922	Rest No meat Drugs	3	7	Dizziness Tinnitus aurium Blurred vision Irritability	160	64	80	72	597	606	16	15	—	—	120	202	120	168	100	4 wks.	0	Very little improvement. Irritability continued.
1164	M	51	June 18, 1922	Low protein Bleeding Drugs Rest	1	6	Headaches Gastritis	170	71	75	64	606	573	24	50	—	—	143	230	150	120	80	2 wks.	0	Headaches disappeared. Condition good. Follows salt-free diet. Albuminuria on admission; disappeared in 6 months. Gastric disturbances ceased.
1182	F	53	July 12, 1922	Drugs Digitalis	2	5	Weakness Dizziness Palpitation Headaches Dyspnea	150	59	53	52	589	568	18	21	—	—	154	170	120	140	92	1 wk.	0	Dyspnea and dizziness relieved.
1230	F	47	Sept. 10, 1922	Drugs Low protein	3	3	Dizziness Weakness	160	63	78	74	594	585	24	30	—	—	132	234	120	190	100	3 wks.	0	Not improved.
1241	M	48	Oct. 1, 1922	No meats	9	2	Headaches Fatigue Pain in legs Slight edema	168	69	73	72	589	601	26	20	—	—	142	184	100	140	84	2 das.	0	Relieved of headaches. Edema disappeared. Vision improved.
1242	M	63	Oct. 1, 1922	No meats	10	2	Nocturia Orthopnea Asthmatic attacks	175	76	67	59	586	589	26	34	+	+	113	182	130	144	88	10 das.	0	Ascites relieved. No asthmatic attacks. General improvement.
1246	M	57	Oct. 4, 1922	Low protein Colon irrigations	4	2	Fatigue Headaches	170	72	89	84	593	581	20	27	—	—	160	214	100	172	100	2 wks.	2	Slightly improved. Still complains of weakness and fatigue.
1268	M	50	Nov. 3, 1922	Teeth extracted No meats	2	1	Gastritis Headaches Pain in arms and legs	184	80	98	93	614	595	18	22	+	+	123	192	100	156	80	3 das.	0	Under treatment. Follows careful diet. Relieved of headaches.
2008	F	46	Jan. 29, 1922	No meats Milk diet Amyl nitrite	2	11	Flushes Blurred vision Paraplegia Paresthesia Palpitation	152	60	59	58	597	564	24	32	+	+	122	202	100	170	100	4 mos.	0	Relieved of flushes and palpitation. Careless at first with return of vascular crises. Now follows strictly salt-free diet.
2009	M	52	Feb. 4, 1922	No coffee or meat	3	11	Palpitation Nocturia Headaches Insomnia	173	74	64	64	581	593	28	40	—	—	118	187	100	162	80	2 wks.	0	Clearer mentally. Follows accurate diet.

TABLE A. *(Continued).*

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	LABORATORY FINDINGS: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	BLOOD PRESSURE: Before Treatment: Systolic	Before Treatment: Diastolic	After Treatment: Systolic	After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
2023	F	59	March 29, 1922	Thyroid extract	....	9	Dyspnea Nocturia	158	63	108	98	601	536	40	12	—	—	143	208	94	144	94	3 wks.	2	Improved.
2080	F	53	June 16, 1922	No meats Potassium iodide	7	6	Angina pectoris Fainting spells Tinnitus Blurred vision	150	59	83	78	589	554	32	28	+	+	109	186	124	182	110	2 mos.	2	Unimproved. Tinnitus and dizziness continued.
2085	M	51	June 19, 1922	No tobacco No alcohol Undernutrition	1	6	Angina pectoris Dizziness Shortness of breath Headaches	185	87	86	82	606	554	14	14	—	—	151	160	85	130	90	3 mos.	2	Headaches disappeared. Improved. Phthalein 55%. Follows careful diet.
2094	F	53	June 30, 1922	No meat	5	6	Weakness Headaches	151	59	71	68	583	564	30	24	+	+	135	230	116	192	104	5 wks.	0	Unimproved.
2142	F	49	Sept. 29, 1922	No meat Undernutrition	4	3	Headaches Weakness Dizziness	173	73	82	81	640	599	14	40	+	+	184	190	116	164	90	3 wks.	0	No improvement symptomatically.

Cases of hypertension with plasma chlorides below 580 mg. per 100 cc.

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	Laboratory Findings: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	Blood Pressure: Before Treatment: Systolic	Blood Pressure: Before Treatment: Diastolic	Blood Pressure: After Treatment: Systolic	Blood Pressure: After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration cm. per day	REMARKS
74	M	40	Oct. 17, 1919	Low protein Purgatives	6	12	Vertigo Tinnitus aurium Blurred vision Headaches	170	65	69	62	565	575	21	14	+	+	105	234	160	215	140	1 yr.	0	Intractable case. Slight improvement of vision temporarily. Phthalein 64%. Died October, 1920.
399	F	49	Dec. 29, 1920	Potassium Iodide Hydrotherapy	1	24	Dizziness Dyspnea	168	69	66	66	527	581	18	20	—	—	190	180	95	143	95	1 mo.	3	Symptomatically improved.
435	M	60	Feb. 3, 1921	Milk diet Potassium iodide	6	23	Fatigue Weakness Nocturia	182	84	74	74	568	577	28	32	—	—	113	210	110	201	120	3 wks.	0	No improvement.
440	M	58	Feb. 1, 1921	Potassium iodide No red meats Hydrotherapy	2	7	Dyspnea Palpitation Angina pectoris Insomnia Edema Amaurosis	170	72	49	41	568	532	24	28	+	+	145	195	114	228	140	2 mos.	0	Improved. Edema and dyspnea disappeared. Relapsed after laxities in diet. Died September, 1921.
470	F	24	Feb. 28, 1921	Low protein Purgatives	2	22	Headaches Blurred vision Precordial pain Insomnia	170	63	54	54	575	585	26	26	+	+	81	220	145	236	140	3 mos.	0	No improvement. Highly neurotic.
507	M	41	Feb. 17, 1921	No meats	2	22	Headaches Fatigue Dyspnea	182	83	89	87	564	563	26	24	—	—	98	182	118	146	95	1 wk.	0	Improved strength.
522	F	50	March 22, 1921	Rest Colon irrigations Nitroglycerine Massage	7	21	Headaches Flushes Nocturia	165	67	62	60	575	583	30	30	—	+		226	118	168	97	10 das.	0	Improved. Careful for five months, then lost from observation.
556	M	46	May 19, 1921	Undernutrition No eggs or meat Potassium Iodide	5	19	Impaired vision Dyspnea Precordial distress			77	75	542	568	23	27	+	+	132	222	140	225	140	1 mo.	0	No improvement. Severe case with advanced arteriosclerosis.
696	M	63	Sept. 4, 1921	No tobacco	2	16	Angina pectoris Palpitation	163	66	70	66	562	568	28	38	—	—	182	222	108	220	110	3 wks.	2	Improved. Follows fairly accurate diet.
794	M	55	Aug. 4, 1921	Low protein Rest	4	17	Angina pectoris Paresthesia Palpitation	178	79	80	76	560	566	22	42	—	—	195	198	120	162	100	1 wk.	2	Temporarily improved.
808	M	59	Aug. 10, 1921	Undernutrition Teeth extracted No meats	3	11	Glaucoma Impaired vision Dyspnea	178	79	74	72	577	532	58	26	+	+	134	212	130	200	110	1 yr.	0	Extreme severity. No improvement. Gradual downward progress. Died September, 1922.

TABLE B. *(Continued)*

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	LABORATORY FINDINGS: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	BLOOD PRESSURE: Before Treatment: Systolic	Before Treatment: Diastolic	After Treatment: Systolic	After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
814	M	55	Aug. 12, 1921	Digitalis No meats Purgatives	4	16	Dyspnea Vertigo Precordial pain	173	74	65	66	532	556	20	40	+	+	125	200	120	185	90	1 mo.	0	Dyspnea improved. Heart became more regular in force and rhythm.
821	M	61	Aug. 16, 1921	No meats Rest Low diet	12	16	Precordial pain Angina pectoris Headache	168	70	76	74	532	530	20	20	—	—	129	150	90	146	80	5 mos.	0	Unimproved.
901	M	56	Oct. 10, 1921	No meats Low calorie diet Hydrotherapy	10	14	Paresthesia Precordial pain	180	81	71	69	577	548	36	28	—	—	126	189	94	190	110	1 mo.	0	Intractable case. Not improved.
907	F	56	Oct. 31, 1921	Low protein Digitalis	7	14	Amaurosis Dyspnea Dizziness Palpitation Edema	163	65	65	58	527	552	38	43	+	+	169	212	110	150	90	1 mo.	0	Edema and dyspnea disappeared. Greatly improved.
923	F	55	Sept. 29, 1921	No meats Potassium iodide	1	15	Dizziness Headaches Edema Flushes	173	74	63	63	577	585	20	10	—	—	153	240	135	120	80	8 mos.	0	Headaches and dizziness disappeared. Follows salt-free diet. Relapses frqeuently when diet is not followed carefully.
940	M	56	Oct. 21, 1921	No meats No tobacco or alcohol Teeth extracted	5	14	Headaches Fatigue Dyspnea Palpitation	165	68	74	70	573	564	38	19	—	—	124	180	120	132	82	3 wks.	1	Marked improvement. Relieved of fatigue and headaches. Dyspnea disappeared.
957	F	55	Nov. 11, 1921	Rest Purgatives No meats	1	13	Weakness Headaches Palpitation	160	64	73	71	577	568	25	36	—	—	121	200	110	130	90	1 mo.	2	Headaches disappeared. Improved.
961	M	51	Nov. 14, 1921	Low protein Potassium iodide Sodium nitrite	2	13	Dyspnea Headaches Blurred vision Edema Gastritis	173	74	80	71	577	560	48	20	+	+	91	170	100	110	65	5 wks.	2	Improved. Follows diet. Gastric complaints disappeared.
1050	F	58	Jan. 17, 1922	Rest Purgatives	9	2	Dizziness Weakness Flashes of light	150	59	47	46	548	565	32	32	+	+	178	160	75	168	80	3 wks.	10	Myocardial insufficiency and anemia. Dyspnea relieved. Marked improvement. Abandoned diet. Died March 17, 1922.

1124	M	60	April 13, 1922	Drugs Hydrotherapy	2	6	Fatigue Mental lassitude Nocturia	170	72	75	75	566	577	40	24	—	—	145	220	142	200	118	3 wks.	0	Nocturia ceased. No change in clinical condition. Abandoned treatment May, 1922. Died October, 1922 of apoplexy.
1128	M	59	April 20, 1922	Low protein Rest Drugs	1	8	Dyspnea Precordial distress Paraplegia	.. .		89	89	548	560	14	30	+	+	125	210	110	175	110	4 mos.	0	Improved. Dyspnea relieved.
1144	F	40	May 5, 1922	Rest Low protein Amyl nitrite	10	7	Dizziness Headache Fatigue Nausea Angina pectoris	163	63	55	55	556	560	24	26	+	+	108	215	125	206	125	2 mos.	0	Not improved.
1154	F	50	May 29, 1922	Drugs	3	6	Headaches Dizziness Weakness Palpitation	150	59	88	80	560	550	30	22	—	—	157	220	160	212	110	4 wks.	0	Not improved.
1210	M	52	Aug. 17, 1922	Drugs Rest	3	4	Edema Dyspnea Amaurosis	178	78	96	77	573	507	48	20	+	+	119	175	80	130	80	3 wks.	0	Edema abolished. Condition improved.
1222	M	53	Sept. 5, 1922	Digitalis Teeth extracted	4	3	Fatigue Nocturia	173	74	82	74	573	583	24	16	—	—	226	220	110	138	80	3 wks.	2	Generally improved. Follows strict diet.
1227	M	47	Sept. 13, 1922	Rest Hydrotherapy	½	3	Precordial pain Fatigue Anesthesia of finger Dyspnea	165	67	59	57	532	544	54	30	+	+	137	256	134	210	150	3 mos.	0	Severe case. Prognosis poor. Temporarily relieved.
2041	M	60	March 14, 1922	No meat No alcohol No tobacco Starvation Digitalis	4	9	Palpitation Flushes Headaches Gastritis	180	81	73	72	568	523	20	20	—	—	133	197	97	194	100	4 mos.	0	Headaches relieved.
2053	M	39	April 11, 1922	Low protein Hydrotherapy Milk diet	4	8	Gastritis Precordial pain Irritability Nervousness	166	65	70	70	564	564	44	10	—	—	159	220	140	210	140	2 wks.	0	Unimproved. Lost from observation.
2057	M	46	April 20, 1922	No meats	1	8	Headaches Dizziness Nocturia Weakness	168	69	54	54	513	515	38	12	+	+	115	220	130	240	106	1 wk.	0	Hopeless severity. Unimproved.
2105	F	55	July 17, 1922	Teeth extracted No meat	2	5	Tinnitus aurium Irritability Dyspnea	165	67	69	67	552	593	38	44	—	—	123	200	100	138	80	2 wks.	0	Symptomatically improved. Relieved of dyspnea and irritability.

TABLE C.

Cases of hypertension with nephritis.

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	Laboratory Findings: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	Blood Pressure Before Treatment: Systolic	Blood Pressure Before Treatment: Diastolic	Blood Pressure After Treatment: Systolic	Blood Pressure After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
13	M	64	July 28, 1919	Digitalis Nitroglycerin Protein-free diet	1	10	Amaurosis Dyspnea Edema Nocturia Headaches	170	72	71	60	556	540	69	198	+	+	94	212	104	166	85	.....	0	Anasarca disappeared on salt-free diet. Arteriosclerosis. Faithful to treatment for 4 months, then abandoned diet. Died May 26, 1920, myocardial insufficiency
41	M	33	Aug. 17, 1919	Low protein diet Restricted carbohydrate	1	22	Weakness Dyspnea Loss of weight Edema	170	68	40	37	648	541	134	99	+	+	176	202	140	140	100	3 wks.	2	Mitral insufficiency, chronic myocarditis. Condition improved. Dyspnea and palpitation relieved. Died August, 1921 of myocardial decompensation.
48	M	42	Sept. 5, 1919	Protein-free diet Digitalis	2	39	Dyspnea Weakness Edema	165	66	61	60	578	624	....	16	+	+	.....	215	170	188	150	5 mos.	0	Chronic myocarditis. Mitral insufficiency. Ascites diminished only slightly after 5 months' treatment.
52	M	45	Sept. 29, 1919	Nitroglycerin Hydrotherapy	5	5	Headaches Polyuria Angina pectoris Palpitation Insomnia Gastritis	171	66	67	57	576	524	55	20	+	+	138	235	145	182	100	5 mos.	0	Cardiac hypertrophy. Temporarily improved. Died February 7, 1920 of uremia.
89	M	62	Nov. 17, 1919	Low protein Restricted activity	2 mo.	37	Palpitation Sudden blindness Anginal attacks Dizziness	170	74	63	61	620	590	20	14	+	+	319	222	90	164	80	.....	0	Phthalein 36%. Refractory case. Pressures lowered but little. Symptomatically improved.
90	M	46	Nov. 19, 1919	Purgatives	6	28	Blindness Palpitation Headaches Dyspnea Edema	178	78	64	58	659	588	104	135	+	+	180	198	100	130	80	1 yr.	0	Moderately severe diabetes with cataracts, retinitis, and gangrene on admission. Careful with diet. Strength improved. Died March 1922, of cardiac insufficiency.
377	F	23	Dec. 9, 1920	Venesection Restricted protein Abortion	8 mo.	24	Headaches Dyspnea Nocturia	152		42	42	581	550	30	80	+	+	120	225	120	256	150	5 mos.	0	No improvement. Severe case in terminal stage. Hypertrophy and dilatation of heart. Secondary anemia. Downward progress.

408	M	61	Dec. 30, 1920	Rest Low protein	4	1	Dyspnea Weakness Loss of weight Fatigue	183	83	55	55	601	544	44	40	+	+	131	218	120	212	134	1 mo.	0	Temporarily relieved. Hopeless case. Died January 28, 1921 of myocardial failure.
434	F	29	Jan. 29, 1921	Low protein Purgatives	1	5	Weakness Headaches Blurred vision	158	57	35	35	601	626	46	146	+	+	121	178	86	165	80	3 mos.	0	Severe case in terminal stage. Edema cleared with temporary general improvement. Relapses. Readmitted May, 1921. Died June 21, 1921 of uremia.
517	F	30	April 18, 1921	Restricted protein	1	20	Weakness Dizziness Dyspnea	170	65	52	52	585	564	90	18	+	—	104	208	135	132	93	7 wks.	0	Temporarily improved. Pyelitis. Retinitis. Severe case. Relapse.
521	M	37	March 11, 1921	Colon irrigations Low protein Drugs	2	14	Dizziness Weakness Edema Amaurosis	.....	....	145	125	606	536	62	114	+	+	.....	204	130	162	110	1 yr.	2	Severe case. Severe anemia. Edema and ascites on admission; relieved. Progress good; relieved of headaches and dyspnea first year. Died May 21, 1922.
572	M	40	Nov. 11, 1921	Rest Low protein	2 mo.	3	Headaches Impaired vision Nocturia	.....	....	65	65	573	589	112	240	+	+	100	190	130	144	80	2 wks.	0	Relieved of headaches within a few days. Improved while under observation. Died Feb. 1922.
847	M	62	Oct. 11, 1921	No meats	1	26	Headaches Dyspnea Edema Amaurosis	182	84	73	69	433	568	64	46	+	+	333	240	140	160	100	1 mo.	0	Edema disappeared. Vision improved. Marked improvement.
978	M	56	Dec. 12, 1921	No meat	2	1	Dyspnea Nocturia Tinnitus aurium Insomnia	152	61	61	58	614	546	244	312	+	+	169	210	110	200	72	18 das.	5	Hopeless severity. Died January 1, 1922 of uremia.
1049	M	35	Jan. 16, 1922	Low protein	3	12	Precordial pain Dyspnea	163	63	54	52	585	560	98	104	+	+	142	210	140	240	140	4 wks.	0	No improvement.
1090	M	37	Jan. 27, 1922	Venesection	1	10 das.	Amaurosis Dyspnea Headaches Nocturia	178	76	64	64	598	581	223	408	+	+	223	194	110	200	120	9 das.	10	Hopeless severity. Died February 6, 1922 of uremia.
1097	M	47	Feb. 13, 1922	Low protein Mineral water	3	10	Palpitation Precordial distress Headaches	175	75	65	64	564	552	46	40	+	+	168	240	140	230	150	8 das.	0	Not improved.

TABLE C. *(Continued)*

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	LABORATORY FINDINGS: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	BLOOD PRESSURE: Before Treatment: Systolic	Before Treatment: Diastolic	After Treatment: Systolic	After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
1130	M	44	April 23, 1922	Low protein	1	8	Dizziness Weakness Dyspnea Amaurosis	180	80	62	57	548	544	34	38	+	+	187	246	162	274	190	1 wk.	0	Hypertrophy of heart. Severe anemia. Hopeless severity. Edema and dyspnea disappeared. Temporarily relieved.
1153	M	57	May 24, 1922	No meat No tobacco Rest Digitalis	2	4	Dyspnea Cough Edema Amaurosis	163	66	64	54	597	527	38	10	+	+	208	160	100	140	90	1 mo.	0	Severe case with cardiac insufficiency. Improved for 4 months. Plasma chlorides always less than 550. Relapsed. Myocardial insufficiency recurred. Died September, 1922.
1155	M	37	May 30, 1922	Rest Venesection Sodium nitrite	2	5	Headaches Precordial pain Fatigue Pain in legs	158	66	59	58	544	540	44	64	+	+	104	200	162	190	120	3 mos.	0	Headaches relieved. Generally improved while diet was carefully observed. Relapsed. Died October 21, 1922.
1158	M	59	June 6, 1922	Low protein Digitalis Purgatives	1	7	Dizziness Headache Fatigue Insomnia	178	79	75	73	573	591	28	54	—	—	126	168	90	160	80	2 mos.	0	General improvement. Less fatigue. Relieved of insomnia.
1160	M	58	June 8, 1922	Low protein Violet rays Digitalis Saline water	4	6	Weakness Dizziness Dyspnea	173	74	68	56	559	534	34	36	+	+	189	160	80	110	60	12 das.	0	Myocardial insufficiency. Severe case. Emaciation. Dyspnea. Ascites cleared. Definitely improved.
1198	F	53	Aug. 6, 1922	No meats Digitalis	6 mo.	3	Dyspnea Headaches Weakness Amaurosis	165	67	76	51	556	527	62	58	+	+	405	210	140	152	96	4 wks.	0	Loss of weight due to elimination of retained fluids. Followed diet for 3 months, then abandoned diet and relapsed. Died November 19, 1922 of pulmonary edema.
1236	M	58	April 23, 1922	Low protein Drugs	3	3	Vertigo Palpitation	.....	....	76	75	587	589	24	30	+	+	121	180	82	225	130	10 das.	0	Cardiac hypertrophy and dilatation. Neurasthenia. Not improved.
1247	M	55	Oct. 5, 1922	No red meats No tobacco	2	3	Headaches Fatigue	185	87	89	87	560	560	64	20	+	+	319	200	114	190	108	1 wk.	0	Follows careful diet. Symptomatically improved.

1258	M	56	Oct. 16, 1922	Rest No tobacco Low protein	4	2	Amaurosis Shortness of breath Weakness Swelling of limbs	175	76	99	87	564	573	54	20	+	+	173	140	110	136	90	8 das.	0	Relieved of ascites and dyspnea. Definitely improved. Follows strict diet. Good result.
1259	M	54	Oct. 24, 1922	Low protein Rest Iodides	3	2	Weakness Fatigue Blurred Vision	175	76	72	69	589	591	20	32	+	+	150	232	140	200	130	3 wks.	0	Dyspnea relieved. Condition improved. Advanced case. Prognosis poor.
2003	M	47	Jan. 17, 1922	Low protein Hydrotherapy Saline purgatives	8	12	Dyspnea Precordial distress Angina pectoris Headaches	165	67	79	75	585	573	46	34	+	+	150	220	140	200	140	3 wks.	0	Cardiac hypertrophy. Angina pectoris Not improved.
2013	M	67	Feb. 10, 1922	Rest Mineral water No tobacco	5	6 das.	Weakness Loss of weight	158	63	64	64	610	618	46	37	+	+	319	200	110	140	100	6 das.	2	Cerebral hemorrhage. Acidosis. Admitted in terminal stage. Died Feb. 16, 1922 of apoplexy.
2054	M	33	April 12, 1922	Colon irrigations Low protein	6 mo.	7	Palpitation Headaches Vertigo	180	77	68	63	626	560	72	16	+	+	136	180	190	172	112	4 wks.	0	No improvement. Died September 11, 1922.
2079	F	47	June 16, 1922	Nitroglycerin Low protein	9 mo.	6	Headaches Weakness Loss of weight	143	56	53	49	548	552	26	28	+	+	469	278	100	160	90	6 wks.	0	Improved. Careful with diet. Systolic pressure at home less than 170.
2107	M	23	July 21, 1922	Low protein Saline purgatives	2	1	Sudden blindness Headaches Angina pectoris Vomiting Edema	178	70	55	54	544	503	86	362	+	+	192	220	120	150	90	5 wks.	5	Severe case with cardiac hypertrophy. Retinitis. Anemia. Died of uremia August 30, 1922.
2125	F	47	Aug. 19, 1922	No meats	2	4	Nocturia Weakness Tinnitus Dyspnea	155	60	70	66	573	546	66	42	+	+	349	218	132	166	100	5 wks.	0	Bulbar paralysis and hemiplegia at admission. Dyspnea relieved. Improved.

TABLE D.

Cases of hypertension with diabetes.

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case: Before Adm. Yrs.	Duration of Case: After Adm. Mos.	Symptoms	Height cm.	Body Weight kg.: Std. Normal	Body Weight kg.: Before Adm.	Body Weight kg.: Final	LABORATORY FINDINGS: Plasma NaCl mg. per 100cc.: Initial	Plasma NaCl mg. per 100cc.: Final	Blood Urea mg. per 100cc.: Initial	Blood Urea mg. per 100cc.: Final	Other Tests at Admission: Albumin	Other Tests at Admission: Casts	Other Tests at Admission: Plasma Sugar mg. per 100cc	BLOOD PRESSURE: Beore Treatment: Systolic	Beore Treatment: Diastolic	After Treatment: Systolic	After Treatment: Diastolic	Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
26	F	50	Aug. 4, 1919	Drugs	2	41	Dyspnea Weakness Loss of weight	175	77	67	61	597	591	37	26	—	—	188	195	92	176	100	.....	0	Improved.
47	F	52	Sept. 4, 1919	Diabetic diet, with undernutrition	4	40	Palpitation Headaches Vertigo Nocturia	170	71	63	56	580	590	43	23	+	+	347	220	140	164	80	.....	0	Pressure low when faithful to diet. Moderately severe diabetes. Improved
73	F	61	Oct. 17, 1919	Rest	4	38	Loss of weight Weakness Hazy vision	152	60	68	64	564	562	27	27	+	+	319	210	100	164	80	2 wks.	0	Improved.
112	F	49	Dec. 13, 1919	Low carbohydrate Rest	3	36	Dizziness Palpitation Tremor	165	67	55	54	597	611	27	20	+	+	147	190	90	130	70	8 das.	0	Improved. Careless with diet.
140	F	60	Feb. 2, 1920	Rest Digitalis Potassium iodide	6	35	Impaired vision Loss of weight Palpitation	158	63	....	....	624	565	28	28	+	+	225	195	115	188	100	2 yrs.	0	Improved. Occasional relapses.
158	F	66	Feb. 19, 1920	Potassium iodide Rest	12	35	Failing vision Headaches Dyspnea Polyuria	160	64	82	75	595	578	16	24	+	+	291	198	100	160	80	6 mos.	2	Dyspnea and headaches relieved. Careless with diet.
212	F	63	March 30, 1920	Colon irrigations Rest Digitalis	1	33	Neuritis Failing vision Senile dementia	168	70	59	56	560	510	20	38	+	+	394	180	70	120	70	3 wks.	0	Improved. Complicated by arteriosclerosis and senile dementia.
244	F	48	May 6, 1920	Low diet	3	31	Loss of weight Weakness Dizziness Tremor	170	74	62	58	578	558	14	22	—	—	315	216	120	158	72	3 wks.	2	Difficult case. Improved.
259	F	40	May 21, 1920	Rest	2	31	Palpitation Tremor Nocturia Depression	160	61	69	62	590	565	13	16	—	—	185	185	100	162	97	2 yrs.	0	Exophthalmic goitre and tachycardia. Condition improved. Faithful to diet.
265	F	40	May 28, 1920	Digitalis	4	15	Gangrene of toe Edema of leg Blurred vision	165	65	61	57	570	568	24	18	+	+	362	186	90	126	70	2 wks.	0	Improved. Abandoned diet. Relapsed. Edema reappeared. Died August, 1921.

300	F	60	July 20, 1920	Reduced diet	4	29	Nervousness Weakness	152	60	57	55	585	580	24	21	—	—	179	160	80	168	85	1 mo.	2	Not improved. Careless with diet.
301	M	58	July 13, 1920	Digitalis Rest Nitroglycerin	1	5	Dizziness Dyspnea Weakness Headaches Ascites	163	66	65	59	575	525	50	40	+	+	201	202	130	140	85	1 mo.	0	Broke diet at every opportunity. Return of edema. Died December 22, 1920 of cardiac insufficiency.
376	F	54	Dec. 8, 1920	None	3	24	Angina pectoris Nocturia Fatigue	170	72	75	75	577	564	26	28	—	—	241	250	110	240	135	2 mos.	0	Intractable case. Advanced arteriosclerosis. Anginal attacks persisted. Condition not improved.
441	F	60	Feb. 12, 1921	Sodium bicarbonate for 2 years Low carbohydrate diet	5	22	Headaches Sciatica	168	70	57	53	593	618	34	39	—	—	188	195	100	156	78	1 mo.	2	Improved.
457	F	56	Feb. 8, 1921	Low protein Digitalis	4	22	Edema Dizziness Fainting spells Palpitation Fatigue	165	67	53	50	608	568	22	38	—	+	151	230	110	156	80	3 wks.	2	Gained strength. Dyspnea, weakness, and edema relieved. Markedly improved.
495	F	52	March 23, 1921	Digitalis Nitroglycerin	3	21	Nocturia Angina pectoris Weakness Neuritis	173	74	78	75	610	562	27	27	—	—	311	192	100	136	70	2 wks.	2	Unimproved. Abandoned diet. Lost from observation.
504	M	55	Feb. 17, 1921	Electrotherapy	2	22	Headaches Weakness Paresthesia	178	79	73	70	634	571	12	25	—	—	219	172	83	128	80	5 das.	5	Follows accurate diet. Pressures remain normal. Improved.
515	F	57	April 16, 1921	Potassium iodide	3	20	Palpitation Weakness Headaches	170	72	70	64	601	558	29	30	—	—	.....	192	110	122	70	1 mo.	1	Pressures remain normal. Improved.
525	F	57	April 17, 1921	Low protein	1	20	Loss of weight Pruritus vulvae Weakness Flushes	170	72	55	54	598	540	28	36	—	—	246	192	100	136	77	1 wk.	4	Headaches and dyspnea relieved. Improved. Follows careful diet.
536	F	42	April 30, 1921	Digitalis Rest	2	20	Headaches Dizziness Weakness	170	69	71	73	582	573	26	22	—	—	230	211	110	140	96	1 wk.	2	Improved. Relieved of headaches and dizziness. No relapses.
558	F	52	May 20, 1921	Rest	3	19	Headaches Weakness Nocturia Palpitation	163	65	64	63	544	578	27	24	—	—	372	214	100	132	80	1 wk.	2	Improved. Careless with diet. Relapse. Lost from observation.

TABLE D. *(Continued)*

Case No.	Sex	Age at Adm. Yrs.	Date of Admission	Treatment Before Admission	Duration of Case		Symptoms	Height cm.	Body Weight kg.			LABORATORY FINDINGS							BLOOD PRESSURE				Length of Treatment Required	Final NaCl Ration gm. per day	REMARKS
					Before Adm. Yrs.	After Adm. Mos.			Std. Normal	Before Adm.	Final	Plasma NaCl mg. per 100cc.		Blood Urea mg. per 100cc.		Other Tests at Admission			Before Treatment		After Treatment				
												Initial	Final	Initial	Final	Albumin	Casts	Plasma Sugar mg. per 100cc	Systolic	Diastolic	Systolic	Diastolic			
597	F	63	May 5, 1921	Purgatives Potassium iodide Rest	4	19	Dizziness Weakness Dyspnea	163	65	73	70	548	552	20	22	+	+	214	187	97	200	80	5 mos.	0	Not improved. Advanced arteriosclerosis and cardiac hypertrophy.
662	F	60	July 23, 1921		1	10	Weakness Precordial pain Indigestion	163	65	63	62	568	550	30	25	+	—	500	160	60	220	110	8 mos.	2	Pressures averaged from 160 to 172 systolic. Not improved. Died April, 1922.
717	F	64	June 17, 1921	Potassium iodide Electrotherapy	2	18	Paralysis Tinnitus aurium	158	63	65	62	555	565	37	30	+	+	.....	196	70	210	126	3 wks.	0	Not improved. Severe case with hemiplegia, chronic. Careless with diet.
754	F	58	July 1, 1921	No red meats	5	18	Dizziness Headaches Blurred vision	175	76	69	59	582	577	37	22	—	—	.....	180	100	140	90	3 wks.	5	Improved. Advanced retinitis. Vision improves when strictly salt-free diet is followed.
874	F	55	Sept. 30, 1921	Potassium iodide Rest	2	15	Weakness Dizziness Palpitation Headaches	158	63	61	50	568	544	30	30	—	—	.....	210	104	180	100	9 mos.	2	Not improved. Arteriosclerosis with myocarditis.
980	F	58	Dec. 20, 1921	Hydrotherapy Electrotherapy Drugs	2	12	Weakness Headaches	178	78	70	66	573	568	20	20	—	—	500	170	90	132	80	2 wks.	2	Improved. Relieved of dyspnea and headaches.
990	M	53	Jan. 4, 1922	Rest No tobacco Drugs	4	12	Headaches Palpitation Nocturia	165	68	77	75	608	585	26	26	+	+	230	170	100	180	100	3 mos.	0	Not improved. Hemiplegia of long standing. Advanced arteriosclerosis.
1057	F	62	Jan. 25, 1922	No meats	5	11	Neuritis Insomnia Fainting spells Dizziness	155	63	64	61	515	610	22	30	—	—	306	202	110	150	86	8 das.	1	Improved.
1059	M	50	Jan. 26, 1922	No meats No tobacco	3	11	Irritability Fatigue Weakness	170	71	75	68	585	593	36	62	+	+	209	194	120	134	90	3 wks.	1	Improved. Relieved of headache.
1066	F	43	Jan. 4, 1922	Rest Drugs	3	11	Weakness Carbuncles Loss of weight Edema	150	....	80	55	564	612	26	26	—	—	453	180	100	130	75	3 mos.	3	Improved. Edema disappeared. Follows salt-free diet.
1098	M	55	Jan. 31, 1922	Potassium iodide Rest	1	11	Loss of weight Headaches Dizziness	165	68	63	56	581	568	26	24	+	+	152	200	120	150	100	16 das.	2	Improved. Follows careful diet. Blood pressure below 150 systolic since discharge.

1163	F	60	June 15, 1922	Rest Purgatives	3	6	Weakness Nocturia	147	50	52	52	579	587	16	12	—	—	385	200	110	170	100	5 wks.	0	Not improved. Careless with diet.
1174	F	59	June 29, 1922	Mineral water Violet rays	6	6	Weakness Carbuncles Fatigue	158	63	73	65	536	544	18	....	—	—	385	190	110	140	62	5 das.	3	Carbuncles on admission; healed. Follows accurate diet. Nocturia and weakness relieved. Improved.
1176	F	66	July 15, 1922	Potassium iodide Rest	5	5	Weakness Pain in arms Nocturia	151	60	61	59	585	589	41	34	—	—	536	190	110	130	60	6 wks.	2	Not improved symptomatically. Lost from observation.
1187	M	65	July 19, 1922	Mineral water No meats Hydrotherapy	2	5	Weakness Pain in arms Precordial pain Angina pectoris	165	68	63	59	577	571	20	46	—	—	214	210	110	150	90	6 wks.	0	Not improved clinically. Complicated by arteriosclerosis and angina pectoris.
1196	M	64	Aug. 3, 1922	Drugs No meats	½	5	Fatigue	168	70	71	64	614	556	40	30	+	+	138	190	85	132	80	4 das.	3	Improved. Follows careful diet. Systolic pressure below1 40 since discharge. Underwent prostatectomy satisfactorily.
2001	M	62	Jan 18, 1922	No meats	1	11	Fatigue Dyspnea Palp tation Paresthesia	163	66	77	71	577	548	16	32	—	—	150	168	110	170	80	2 mos.	0	Not improved. Careless with diet. Excessive diet.
2032	F	57	March 1, 1922	No meats	3	10	Dyspnea Weakness Tinnitus No meats	.....	....	57	56	610	590	63	24	—	—	270	180	90	126	72	10 das.	0	Ignorant patient. Diabetes moderately severe. Good result when on diet.
2076	F	49	July 12, 1922	Potassium iodide Rest	3	5	Weakness Pruritus Dizziness	150	59	50	49	597	577	40	31	—	—	.....	190	100	150	90	6 wks.	1	Not improve l.
2113	F	52	Aug. 14, 1922	Undernutrition	1	4	Weakness Pain in shoulders	143	57	57	53	577	572	48	30	—	—	113	160	100	134	80	5 das.	2	Follows rigid diet. Systolic pressure below 150 since discharge.
2114	F	58	Aug. 4, 1922	Rest	4	4	Weakness Pain in shoulders Paresthesia	155	61	60	56	548	577	22	36	—	—	326	212	110	150	80	4 das.	2	Follows careful diet. Symptomatically relieved.
2153	F	65	Oct. 16, 1922	Low protein Undernutrition Mineral water	5	2	Pain in legs Weakness Fatigue Dizziness	150	59	55	53	616	590	52	30	—	—	130	170	90	155	78	12 das.	1	Improved.

PREFACE

This issue of the Journal of Metabolic Research contains the first detailed reports of the clinical use of insulin. After the application of this new discovery to the practical treatment of patients in the Medical Department of the University of Toronto and the preliminary announcements of the beneficial results (see review in the August, 1922, number of this Journal, and a later publication by Banting, Campbell and Fletcher in the British Medical Journal for January 6, 1923), arrangements were made whereby insulin manufactured by the Eli Lilly Company of Indianapolis was distributed to an informally organized committee in the United States, composed of Drs. R. T. Woodyatt, J. R. Williams, R. M. Wilder, E. P. Joslin, H. R. Geyelin, and F. M. Allen, for further therapeutic trials and experimental studies. As the supply of insulin at first was very small, it was considered that by this means the most information would be gained and the least danger encountered during the time which must elapse before the solution of the difficult problem of the large-scale preparation of insulin in a potent, stable and standardized form should permit placing it on the market. As the production of insulin has increased, a gradually increasing number of physicians or clinics in this country have received it from the Eli Lilly Company under supervision of the Insulin Committee of the University of Toronto.

Owing to delays in the publication of this Journal, the present issue, though nominally for November-December, 1922, actually goes to press in May, 1923, and it will be observed to contain records dated accordingly. In the case of similar findings, it is understood that the observations in Toronto are to be regarded as the original ones. All the contributors have worked independently, but through letters and conversations between individuals, and a general discussion at a meeting in Toronto, each has become fairly well acquainted with the views of the others. All manuscripts likewise have been prepared independently, but subsequently the other authors have been furnished with proofs of the three Toronto papers, which are to be regarded and quoted as

prior publications. The dates upon which the respective communications were received were as follows:

R. M. Wilder, W. M. Boothy, C. J. Barborka, H. D. Kitchen, S. F. Adams.	January 29, 1923.
E. P. Joslin, H. Gray, and H. F. Root.	February 2, 1923.
R. Fitz, W. P. Murphy, and S. B. Grant.	February 17, 1923.
J. R. Williams.	February 21, 1923.
A. A. Fletcher and W. R. Campbell.	February 26, 1923.
W. R. Campbell.	March 13, 1923.
F. G. Banting, W. R. Campbell and A. A. Fletcher.	March 17, 1923.
H. R. Geyelin, G. Harrop, M. F. Murray, and E. Corwin.	April 19, 1923.
F. M. Allen and J. W. Sherrill.	April 25, 1923.
R. T. Woodyatt.	May 9, 1923.

INSULIN IN THE TREATMENT OF DIABETES MELLITUS

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In a recent paper, further clinical experience with insulin in the treatment of diabetes mellitus was reported[1]. The tentative conclusions recorded in a preliminary communication in March, 1922[2], have been confirmed. It was also shown that, following the administration of insulin in fifty cases of diabetes mellitus, the cardinal symptoms of the disease are relieved and patients show well marked improvement in their general physical condition and mental outlook. In particular, glycosuria is abolished, ketones disappear from the urine and blood, the blood sugar can be maintained at a normal level, the respiratory quotient rises showing carbohydrate utilization, the alkali reserve and alveolar carbon dioxide of patients in acidosis and coma return to normal. The successful treatment of diabetic coma with insulin was described, together with a new symptom complex—hypoglycemia.

It is the purpose of the present paper to discuss more fully some of the problems which have arisen in the treatment of diabetes mellitus with insulin,* and to report in more or less detail the clinical course and treatment of certain cases. It is hoped that sufficient evidence will be found in the material reported to justify the conclusions reached. Some of these are tentative and no doubt will be confirmed or corrected by subsequent investigation. We trust, however, that certain of the principles of insulin treatment indicated here will serve as a foundation for those about to commence the use of insulin in clinical practice.

The patients admitted to hospital were examined as to their clinical history and physical condition and observed on a definite

* The insulin used in the clinical investigations here recorded was manufactured and supplied by the Connaught Antitoxin Laboratories of the University of Toronto, and the Eli Lilly Co. of Indianapolis.

regime for a limited period. For 48 hours they were kept in bed but afterwards allowed up. No considerable amount of exercise was permitted on account of the rise in metabolism with increased breakdown of body tissues. A diet is served them based upon the normal basal caloric requirement calculated from the Du Bois chart and Aub-Du Bois tables. As excess protein uses up the patient's insulin a protein ration just sufficient to provide for the replacement of the normal tissue breakdown is supplied. Marsh, Newburgh and Holly[6] have shown that, under basal conditions, 2/3 gm. of protein per kg. body weight is sufficient. As amino acids unsuitable for replacement of tissue breakdown are simply burned for their value in terms of energy, it seems desirable to give the protein requirement in the form of the class A proteins, meat, eggs, milk, fish, etc., since unsuitable protein constituents use up insulin during their combustion. The remaining energy requirement must be met by carbohydrate and fat. To avoid ketosis the ratio of the total glucose in the diet to the fat must at least attain a certain minimum—one molecule of glucose to two molecules of fatty acid—as Wilder[8] and Shaffer[7] have shown. Using such high ratios is possible but entails limitation of the variety of food stuffs. From the standpoint of the patient, a diet so at variance with the normal diet must be prepared and served so that it is palatable and appetizing. Diets have been constructed which allow of greater palatability and whose ratio of ketogenic to anti-ketogenic substances is 1.3:1.[3] This ratio obtains when the quantities of fat (F) and of carbohydrate (C) are derived from the following formulae: $F = \frac{M}{10} - \frac{P}{2}$ and $C = \frac{M - 10P}{30}$ where (M) is the normal basal requirement in calories and (P) the protein in grams. The calculated allowance of protein, fat and carbohydrate is apportioned between the various meals and the diet made up in the usual manner.

Recognizing that the results of our investigation must by no possibility be open to question on account of insufficient attention to dietetic factors, particular care has been used to control these. Complete records are kept of the kind and amount of all foods served at various meals, and in many cases absolute constancy of diet as to amount and kind of food and the time of serving. Food is checked on leaving the diet kitchen, and any unused food is weighed and recorded. Atwater's tables, the recent literature and our own analyses are used for calculating diets. Non-nutrient materials if properly prepared, provide bulk and variety and increase the palatability of the diet. Daily qualitative and quantitative examinations of the urine

for sugar, acetone, diacetic acid, and total nitrogen are made as well as the usual routine tests. Blood sugars are taken in the morning with the patient fasting and, as with other tests, when otherwise indicated. Body weight is taken twice weekly before breakfast. The methods used in our investigations we have already noted in our last publication. It may not be amiss to repeat them here: sugar is determined by Benedict's and Shaffer and Hartmann's methods; ketones (acetone and diacetic acid) by Rothera's and Gerhardt's tests and Van Slyke's methods; total nitrogen is determined by a modification of the well-known Kjeldahl method; blood sugar is estimated by the revised Folin-Wu and Shaffer-Hartmann methods; blood ketones by Van Slyke's methods; carbon dioxide combining power of the blood by Van Slyke's method; alveolar air carbon dioxide by Marriot's method and a modification of Haldane's method, similar to Roth's; basal metabolism and respiratory quotients are determined by the Douglas-Haldane and Tissot-Haldane methods. Many of these chemical methods are not necessary for the actual clinical treatment of a diabetic patient but are useful for a metabolic study of the disease.

A majority of patients have shown well marked glycosuria and hyperglycemia on this regime and often acidosis or other complications. We have no doubt that a few of them could have been made aglycosuric by starvation treatment, but the advisability of doing so in these severely undernourished individuals is certainly open to question. We do not think it would have affected the question as to whether insulin should be used or not, as undoubtedly they could not have been maintained in weight and strength on any diet commensurate with their requirement. The use of diets based on Wilder's K.A. ratio 1.7:1 has been tried in some of these cases, not only on the normal basal caloric requirement for the individual but also on the determined basal metabolism, without success, although other cases have received benefit from it.

Owing to the limited supply of insulin available, patients with sufficient tolerance to maintain themselves aglycosuric, and without hyperglycemia on a diet somewhat above the basal requirement, have been advised to continue dietetic treatment. Patients not adequately controlled by diet, patients in coma or surgical emergencies have been given insulin treatment. The preliminary period of observation permits us to collect much information of value as to the patient's tolerance at rest, the extent of the glycosuria and reaction of the blood sugar to dietetic treatment, the severity of the ketosis or acidosis, and gives opportunities for adjusting the diet to the patient's preferences as far as possible in preparation for the administration of insulin.

The Administration of Insulin

The technical details of the administration of insulin and its local effect perhaps call for some comment. Insulin as received is sterile and must be handled with aseptic precautions. It is drawn into a syringe, sterilized by boiling, by inserting the needle through the cork after first wiping the cork with tincture of iodine. If desired a large needle may be used for withdrawing the insulin from the vial but for injection we prefer very sharp, 27 gauge, 7/8 in. French Record needles. After wiping the skin with alcohol or tincture of iodine the needle is plunged straight through the skin into the subcutaneous tissue. The skin of the diabetic, particularly the patient showing marked emaciation, should be subjected to as little trauma as possible. At the instant of receiving the injection the patient is conscious of the prick of the needle and the pain of distension of the tissues with the fluid. These two effects are negligible provided the injection is skillfully done and the volume of the fluid is small. Injections should not be made into the muscle tissue as this adds largely to the subsequent pain and tenderness and is sometimes followed by induration. Those patients requiring rapid institution of insulin therapy, such as cases of coma, are best treated by the intravenous route.

In the first cases treated the salt content of the pancreatic extracts was very high and, indeed, precipitated out when the extract was kept in the refrigerator. This caused a marked stinging sensation at the site of injection persisting for an hour or more, and steps were taken immediately which overcame this difficulty. At the present time, however, certain samples of insulin have a similar effect, the sting lasting about ten minutes and not at all severe. The further local effect is tenderness over the site of injection and, on this account, injections should be made with a view to avoiding pressure points as the patient feels no pain until the area is touched. This tenderness persists from one to ten hours, varying somewhat with the sample of insulin used. It is usually accompanied by slight induration of the subcutaneous tissue at the site of injection and reddening of the skin immediately surrounding the point of puncture. These effects seem formidable but in reality are not as great as those seen following the injection of pituitrin, caffeine, theocin, digitalin, strophanthin or camphor, and do not compare with the

local effects from doses of vaccines. No serious cases of protein sensitization have been encountered.

Before entering on a description of the method of gauging insulin dosage it may not be amiss to consider some factors in the pathological physiology of diabetes. In this disease we now know the fundamental defect is the failure of the pancreas to produce an adequate amount of insulin. As a result, there is a failure to metabolize or store carbohydrate, and glycosuria occurs. The lack of sufficient carbohydrate in the process of combustion is the cause of failure to burn fats completely, and ketosis and ketonuria ensue. In most cases a diet properly balanced in its proportion of protein, fat and carbohydrate enables the body to get the maximal beneficial effect from the limited supply of insulin: in certain cases additional insulin is required.

Normally, the secretion of insulin is probably a continuous process, greater after the ingestion of carbohydrate. In the artificial administration of insulin it is clinically impossible to imitate this process. When the requirement of insulin is small it may be taken in one dose, preferably before the evening meal in which should be concentrated the greater part of the total glucose of the diet. This method is occasionally useful, but it is not suitable for maintaining low blood sugar levels, particularly in old people with high thresholds. One-half the dose given twice in the day allows a larger utilization of foodstuffs per unit of insulin. As a rule two doses daily, one before breakfast and a second before the evening meal, is preferable. In other cases it may be necessary to give the insulin required in three doses, one before each meal. It is evident that the amount and time of administration of insulin will vary with the individual treated.

The dose of insulin is prescribed in units.* At present two strengths of insulin are supplied—one containing 5 units per c.c., the other 10 units per c.c. As a rough approximation for estimating the dose of insulin for making the patient aglycosuric each unit may be considered as equivalent to 1-1.5 gm. of glucose. During the preliminary period of observation the amount of sugar excreted on a basal diet is determined. If, for example, the patient excretes 40 gm. of glucose, 25 units of insulin may be

* In our earlier paper the dosage of insulin was referred to in cubic centimetres, and one cubic centimetre was supposed to contain approximately one unit. Recently a new system of unitage for insulin has been adopted, in which the units are much smaller. We are aware that there was considerable variation in the potency of the different batches of insulin used in the treatment of the cases here reported. As far as we are able to judge, 1.0 c.c. of insulin used equals 10 units, according to the present method of standardization.

prescribed for the first day's dose. This dose may make the patient aglycosuric on the first or second day and, in this case, the dose is probably more than is required for maintaining him in this condition and may be reduced. If, however, glycosuria persists after the first few days, a small additional amount of insulin may be given. By such a method one gradually makes the patient aglycosuric and decreases the danger of hypoglycemia. As a guard against this, in the early stages of insulin treatment we have a high initial blood sugar level and an excess of sugar in the tissues, which must be burned or excreted before the blood sugar falls to normal. This may require additional insulin, but in certain cases the pancreatic rest attained by diet and insulin may result in an improved tolerance, and the dose of insulin may even be reduced. Though glycosuria may be absent the blood sugar may be too high. As the object of treatment is to maintain a patient not only aglycosuric, but with a normal blood sugar, periodic estimations of the blood sugar are necessary to determine whether or not sufficient insulin is being given.

Insulin in excess of the requirement causes Hypoglycemia,* which may be controlled by increasing the diet, reducing the daily dose or placing a larger portion of the total glucose in the meal next previous to the time of the reaction. Slight excess of insulin tends to produce a reaction 1-5 hours after the last dose of the day. A larger excess may produce a reaction following the first dose of the day. Observation of the fasting blood sugar has been a means of predicting a morning reaction, as it may show a steady fall for some days before the patient is conscious of anything abnormal. As different batches of insulin vary in potency it is our present practice to introduce the new preparation gradually in the following manner:

1. ¼ dose new insulin + ¾ dose old insulin.
2. ½ dose new insulin + ½ dose old insulin.
3. ¾ dose new insulin + ¼ dose old insulin.
4. All new insulin.

The treatment of severe diabetes mellitus by insulin is illustrated in the following case reports:

H. D., male, age 46, married; admitted September 3, 1922; discharged January 8, 1923.

Present illness: In the fall of 1915, after a period of polyuria, his urine

* The symptomatology and treatment of Hypoglycemia is described elsewhere.

was found to contain 7 per cent. sugar. His weight at that time was 135 lb. The glycosuria was relieved by a diet low in carbohydrate, but recurred from time to time during the following winter. In April, 1916, the glycosuria was treated in hospital—two days of starvation and two weeks of a diet of vegetables containing 5 and 10 per cent. carbohydrates. In July, 1918, he was again put on a diet of vegetables only. In November, 1919, he entered the hospital again. Blood sugar on admission .33 per cent. At time of discharge he was free of glycosuria on a diet of 20 gm. of carbohydrate, 65 gm. of protein and 100 gm. of fat. On July 16, 1921, he entered a third hospital. He states that, on admission, his blood sugar was .4 per cent. The following is an extract from his hospital record: July 17; 24 hour specimen of urine, amount 1,600 c.c.; spec. grav. 1,020; sugar 63 gm.; acetone and diacetic acid present in large amounts. Weight 113½ lb. He left hospital on September 1; blood sugar .24 per cent.; diet of 20 gm. of carbohydrate, 86 gm. of protein, 166 gm. of fat. He entered hospital again January 25, 1922. He states his blood sugar was .63 per cent. For three weeks he received less than 400 calories daily. His blood sugar fell to .12 per cent., but subsequently varied from .15 per cent. to .2 per cent. The diet was then gradually increased so that at time of discharge, March 21, 1922, he was allowed carbohydrate, 10 gm., protein, 45 gm., fat about 85 gm. His weight was 98 lb. He complained of extreme weakness. After leaving hospital he increased the protein of his diet very considerably, but, in spite of this, he was not able to regain strength.

Past illness: Pneumonia, 1876 and 1882; typhoid, 1882; measles, whooping-cough, influenza, frequent gastro-intestinal disorders, 1882 to 1892; tonsillitis, 1897, with yearly recurrence; 1904, "nervous breakdown."

Personal history: Born in United States; Hebrew race; attorney-at-law; always high-strung; states he worked intensively, with little recreation or exercise; smokes tobacco to excess; has taken alcohol in moderation.

Family history: No family history of diabetes, obesity or tuberculosis.

Examination: Thin, somewhat pale; weight 107 lb.; strong odor of acetone on the breath; no dyspnea; no drowsiness; skin dry; hunger and thirst excessive. Slight edema present. Very weak and very easily fatigued. He was keen and alert, but prolonged mental effort exhausted him. Digestive system: pyorrhea and dental caries present; abdomen distended; liver palpable. Respiratory system: negative. Cardio-vascular system: vessels not sclerosed; no cardiac enlargement; systolic blood pressure 110, diastolic blood pressure 90; hemoglobin 30 per cent.; Wassermann reaction negative. Nervous system: ankle jerks and knee jerks absent; other muscles jerks present; no disturbance in sensation; pupils active and equal.

Treatment: On September 4, 1922, a diet of protein 32 gm., fat 134 gm., carbohydrate 39 gm. was given and was continued without change to October 26. After the preliminary period of ten days observation 20 units of insulin was given on September 15 and again on the 16th; on September 17, 30 units of a preparation which was not potent. From September 20 to October 18 insulin was given in doses varying from 35

TABLE I—PATIENT H. D.

Date	Urine							Fasting Blood Sug. %	Food Intake				Weight Pounds	Insulin		Batch
	Vol. c. c.	R	Sp. G.	Sug. Gm.	Ketones SNP	Ketones FeCl3	Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	c. c.	
1922																
4/9	2750	..	1022	95.5	P*	P*	14.24	....	32	134	39	1490	107½	.....	..	...
5/9	1850	..	1027	55.5	P	P	13.21	.337	32	134	39	....	.....	.....	..	...
6/9	3400	..	1014	65.8	P	P	12.14	....	32	134	39	....	.....	.....	..	...
7/9	3540	..	1015	63.5	P	P	10.06	.275	32	134	39	....	.....	.....	..	...
8/9	5151	..	1009	64.5	P	P	13.34	....	32	134	39	....	.....	.....	..	...
9/9	3150	..	1011	45.4	P	P	7.50	.331	32	134	39	....	.....	.....	..	...
10/9	4450	..	1008	46.7	P	P	6.45	....	32	134	39	....	117	.....	..	...
11/9	4506	..	1006	32.2	P	P	6.30	.295	32	134	39	....	.....	.....	..	...
12/9	4650	..	1008	40.5	P	P	7.81	....	32	131	39	....	.....	.....	..	...
13/9	4750	..	1006	35.6	P	P	7.32	.275	32	134	39	....	.....	.....	..	...
14/9	5700	H	1006	47.5	P	P	6.39	....	32	134	39	....	.....	.....	..	...
15/9	6050	H	1004	15.6	P	P	6.35	.328	32	134	39	....	.....	8 a. m.	2	120
16/9	5500	H	1005	23	P	0	6.16	.295	32	134	39	....	.....	8 a. m.	2	120
17/9	6750	H	1004	32.5	P	0	5.20	.26	32	134	39	....	....	8 a. m.	3	...
18/9	5250	H	1016	41.5	P	0	5.33	.31	32	134	39	....	116	.....	..	...
19/9	3400	H	1005	37.6	P	0	6.80	.345	32	134	39	....	.....	.....	..	...
														8 a. m.	2	
20/9	6720	OH	1002	8.7	P	0	5.65	.33	32	134	39	....	.....	5 p. m.	2	127
														8 a. m.	2	
21/9	5800	H	1002	0	0	0	6.09	....	32	134	39	....	.....	5 p. m.	2	127
														8 a. m.	2	
22/9	5550	N	1002	0	0	0	.....	.22	32	134	30	1490	.....	5 p. m.	2	127
														8 a. m.	2	
23/9	5700	N	1002	0	0	0	4.79	....	32	134	39	....	.....	5 p. m.	2	127
														8 a. m.	2	
24/9	6540	OH	1004	0	0	0	.....	....	32	134	39	....	.....	5 p. m.	2	127
														8 a. m.	2	
25/9	6760	H	1006	0	0	0	6.62	.208	32	134	39	....	.....	5 p. m.	2¼	127
														8 a. m.	2	
26/9	5100	H	1003	0	0	0	5.67	....	32	134	39	....	116	5 p. m.	2	137
														8 a. m.	2	
27/9	6550	H	1000	0	P	0	.....	.215	32	134	39	....	.....	5 p. m.	2	137
														8 a. m.	2	
28/9	6300	H	1002	3.4	P	0	6.17	....	32	134	39	....	.....	5 p. m.	2	137
														8 a. m.	2	
29/9	6800	H	1004	11.9	P	0	10	.27	32	134	39	....	.....	5 p. m.	2	137
														8 a. m.	2	
30/9	5500	H	1004	0	P	0	8.85	.288	32	134	39	....	.....	5 p. m.	2	137
														8 a. m.	2	
1/10	5950	H	1004	0		0	9.58	....	32	134	39	....	.....	5 p. m.	2	137
					P									8 a. m.	2	
														12 m.	2	
2/10	7450	N	1002	0	0	0	7.82	.305	32	134	39	....	114	5 p. m.	2	139

														8 a. m.	2	
														12 m.	2	
3/10	5400	H	1003	0	0	0	4.91	. .	32	134	39	. . .	. . .	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
4/10	5500	H	1003	0	0	0	5 77	153	32	134	39	. . .	.....	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
5/10	5800	H	1004	0	0	0	5.27	....	32	134	39	. . .	.....	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
6/10	4800	H	1006	0	0	0	6.38	.186	32	134	39	....	.....	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
7/10	6100	H	1004	0	0	0	7 68	....	32	134	39	....	.....	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
8/10	6250	H	1004	0	0	0	5 27	169	32	134	39	....	.....	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
9/10	6725	H	1007	0	0	0	6.35	161	32	134	39	....	115	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
10/10	5495	H	1008	0	0	0	4.93	....	32	134	39	....	.....	5 p. m.	2	139
														8 a. m.	2	
														12 m.	2	
11/10	7200	H	1002	0	0	0	6.5	....	32	134	39	....	.....	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
12/10	5650	H	1001	0	0	0	4.87	.218	32	134	39	....	.....	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
13/10	6750	H	1002	0	0	0	5.2	.188	32	134	39	....	.....	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
14/10	5900	OH	1004	0	0	0	4.54	....	32	134	39	....	.....	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
15/10	7400	H	1006	0	0	0	6.73	.186	32	134	39	....	.....	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
16/10	6200	H	1004	0	0	0	5.20	....	32	134	39	....	...	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
17/10	5800	H	1002	0	0	0	4.87	.123	32	134	30	....	.....	5 p. m.	2	142
														8 a. m.	2	
														12 m.	2	
18/10	6780	H	1004	0	P	0	8 54	....	32	134	30	....	118½	5 p. m.	2	142
19/10	7050	H	. . .	0	P	0	6 4	.122	32	134	30	....	.....	.....	..	...
20/10	7200	H	1004	0	P	0	6.05	....	32	134	39	....	.....	.....	..	...
21/10	6550	H	1008	3.54	P	0	7.14	.225	32	134*	39	....	.....	.....	..	...
22/10	6275	H	1008	6.97	P	P	6 65	.254	32	134	39	....	116½	.....	..	...
23/10	6150	H	1007	6.98	P	0	8.9	.289	32	134	39	....	.....	.....	.	...

* P denotes positive.

TABLE I—PATIENT H. D.—Continued

Date	Urine							Fasting Blood Sug. %	Food Intake				Weight Pounds	Insulin		Batch
	Vol. c. c.	R	Sp. G.	Sug. Gm.	Ketones SNP	Ketones FeCl3	Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	c. c.	
1922																
24/10	4520	..	1007	5 92	P	P	5.7	.288	32	134	39	....	111¼	.....	..	...
25/10	5950	H	1005	7 84	P	O	9 1	.292	32	134	39	....	.....	.....	..	...
26/10	4100	H	1010	28 6	P	P	8 4	.305	50	207	59	....	112½	.....	..	...
27/10	6100	H	1010	45.5	P	P	8 6	.326	50	207	59	....	112½	.....	..	...
28/10	6910	H	1010	45 8	P	P	9.08	.300	50	207	59	2299	110½	.....	..	...
29/10	6050	H	1011	51 6	P	P	.....	.324	50	207	59	....	.....	.....	..	...
30/10	6670	H	1011	58 6	P	P	.....	.360	50	207	59	....	111½	.....	..	...
31/10	6550	H	1011	61 3	P	P	.....	.344	50	207	59	....	.....	.....	..	...
1/11	990	H	1011	48.7	P	P	11.36	.326	50	207	59	....	109	.....	..	...
														8 a. m.	3	
														12 m.	3	
2/11	4710	H	1010	11 26	P	P	.....	.350	50	207	59	....	110½	5 p. m.	3	150
														8 a. m.	3	
														12 m.	3	
3/11	5420	H	1008	0	P	0	15.93	.192	50	207	59	....	113¼	5 p. m.	3	150
														8 a. m.	3	
														12 m.	3	
4/11	6310	H	1007	0	0	0	.....	.187	50	207	59	....	114¾	5 p. m.	3	151
														8 a. m.	3	
														12 m.	3	
5/11	5112	OH	1007	0	0	0	.....	.160	50	207	59	....	.....	5 p. m.	3	151
														8 a. m.	2	
														12 m.	2	
6/11	5150	H	1008	0	P	0	6.49	.189	50	207	59	....	114½	5 p. m.	2	151
														8 a. m.	2	
														12 m.	2	
7/11	5181	H	1009	0	P	0	.....	.198	50	207	59	....	.....	5 p. m.	2	151
29/11	1300	H	1008	0	P	0	.....	....	48	138	48	1626	112	8 a. m.	2	151
30/11	6150	H	1006	0	P	0	12.9	.158	48	138	48	....	.....	8 a. m.	2	156
1/12	5800	H	1005	0	P	0	.....	....	48	138	48	....	.....	8 a. m.	2	156
2/12	.....	..	.....	..	..	..	.....	.197	48	138	48	....	.....	8 a. m.	2	156
8/12	2350	H	1008	0	P	0	.....	....	48	138	48	....	.....	8 a. m.	2	156
														8 a. m.	1	
9/12	4800	H	1010	0	0	0	.....	.246	48	138	48	1626	114½	5 p. m.	1	157
														8 a. m.	1	
10/12	4150	H	1007	0	0	0	.....	....	48	138	48	....	.....	5 n. m.	1	157
														8 a. m.	1	
11/12	3500	H	1008	0	P	0	7.7	.255	48	138	48	....	.....	5 p. m.	1	157
														8 a. m.	1	
														12 m.	1	
12/12	4450	H	1007	0	P	0	.....	....	48	138	48	....	112¾	5 p. m.	2	158
														8 a. m.	2	
13/12	4550	H	1010	0	P	0	7 7	.172	48	138	48	....	114½	5 p. m.	2	158

															8 a. m.	2	
14/12	4550	..	1010	0	P	0	8.6	. . .	48	138	48	....	.....		5 p. m.	2	158
															8 a. m.	2	
15/12	6200	II	1006	0	P	0	.....	.213	48	138	48	....	.....		5 p. m.	2	153
															8 a. m.	2	
16/12	3850	II	1008	0	P	0	7.7	....	48	138	48	....	.....		5 p. m.	2	158
															8 a. m.	2	158
17/12	4600	II	1007	0	P	0	.....	....	48	138	48	....	.....		5 p. m.	2	159
															8 a. m.	2	
18/12	3800	II	1007	0	0	0	....	.207	48	138	48	....	115		5 p. m.	2	159
															8 a. m.	2	
19/12	4200	II	1006	0	P	0	.....	. . .	48	138	48	....	....		5 p. m.	2	159
															8 a. m.	2	
20/12	2850	II	1009	0	0	0	.....	.141	48	138	48	....	.....		5 p. m.	2	159
															8 a. m.	2	
21/12	5000	II	1010	0	P	0	.....	....	48	138	48	....	115½		5 p. m.	2	159
															8 a. m.	2	
															12 m.	2	159
22/12	5000	..	1007	0	P	0	10	.140	48	138	48	....	115½		5 p. m.	2	160
															8 a. m.	2	
23/12	4100	OII	1008	0	0	0	.....	....	56	180	60	2084	....		8 a. m.	2	160
															8 a. m.	2	
24/12	4200	OII	1010	0	0	0	11.2	.146	56	180	60	....	.		5 p. m.	2	160
															8 a. m.	2	
25/12	3750	II	1007	0	0	0	11.3	....	56	180	60	.	115½		5 p. m.	2	160
															8 a. m.	2	
26/12	3400	II	1008	0	P	0	11.2	.137	56	180	60	..	....		5 p. m.	2	160
															8 a. m.	2	
27/12	3600	II	1007	0	P	0	8.3	. .	56	180	60	2084	.....		5 p. m.	2	160
															8 a. m.	2	
28/12	4850	II	1010	0	0	0	11.6	.165	56	180	60	. .	. . .		5 p. m.	2	160
															8 a. m.	2	
29/12	..	..	....	..	..	..	.....	....	56	180	60	. .	116½		5 p. m.	2	166
															8 a. m.	2	
30/12	4400	II	1009	0	0	0	.....	. . .	56	180	60	.	. .		5 p. m.	2	166
															8 a. m.	2	
31/12	4300	II	1007	0	0	0	.....	.204	56	180	60		.....		5 p. m.	2	166
1923															8 a. m.	2	
1/1	4300	II	1007	0	0	0	8.4	....	56	180	60	. .	.....		5 p. m.	2	166
															8 a. m.	2	
2/1	3350	II	1009	0	0	0	8.3	.175	56	180	60	. .			5 p. m.	2	166
3/1	5000	II	1008	0	0	0	9.9	.236	56	180	60	. .	118½		.....	...	
															8 a. m.	2	
4/1	3600	II	1009	1.44	P	0	7.3	....	56	180	60	....	.....		4 p. m.	2	168
															8 a. m.	2	
5/1	4700	II	1006	0	0	0	9.4	.64	56	180	60	....	.....		5 p. m.	2	168
															8 a. m.	1	
6/1	4000	OII	1007	0	0	0	.....	.138	56	180	60	....	.....		5 p. m.	2	168
															8 a. m.	2	
7/1	4150	II	1007	0	0	0	9.7	....	56	180	75	2144	.....		5 p. m.	2	168
															8 a. m.	1	
8/1	....	..	....	..	..	..	.....	....	56	180	60	2084	.....		5 p. m.	1	168

*P denotes positive.

to 60 units. The injections were then discontinued until November 2, when 90 units were given daily for four days and 60 units daily for three days. On October 26 the diet was increased to protein 50 gm., fat 207 gm., carbohydrate 261 gm. He was absent from hospital from November 8 to November 29. During this time his diet was approximately protein 48 gm., fat 138 gm., carbohydrate 48 gm., and he received 40 units of insulin a day. Daily examinations of the urine and occasional fasting blood sugar estimations were made by Dr. Joseph H. Barach of Pittsburg. Dr. Barach was kind enough to send us his results. He returned to hospital on the 29th of November for three days, and again for a third period from December 8 to January 8, 1923. He continued his diet of protein, 48 gm., fat, 138 gm., carbohydrate, 48 gm. until December 23, and from then on 56 gm. of protein, 180 of fat, and 60 of carbohydrate. From November 29 to January 8 insulin was given in amounts varying from 20 to 60 units a day.

General progress: When admitted he was so easily fatigued that practically no physical exercise was attempted. Regular insulin treatment was begun September 20. On the second or third day he referred to a feeling of increased well-being. This might be the result of the clearing up of the ketosis. From the 6th to 12th day the insulin given was low in potency and further progress was not much in evidence. During the second two weeks of insulin treatment much more rapid improvement took place. Especially evident was the increased physical vigor. Even on this diet of 1490 calories he could take walks of four miles in an afternoon without difficulty. He lost his flabby appearance and his general bearing became one of inereased vigor. From October 18 to November 2, the period when insulin was stopped, he retained his feeling of increased strength to a considerable degree, although when the diet was increased on October 26 severe ketosis developed. Insulin administration was resumed on November 2. With this treatment, along with this increased diet, he said he felt in the best of health. He was in very good spirits and so enthusiastic that his actual state of physical fitness could scarcely be gauged. He was not encouraged to take much exercise but he enjoyed what he took. He ate his meals with relish but did not have the insatiable hunger of the diabetic. On November 8 he returned to his home, and for most of the next three weeks he carried on his practice, seeing clients, going into court, and completing some of the work which was in arrears. He stated that his power of application for work of this sort was as good as before the onset of the disease. During the second and third periods in hospital it became evident that his improvement was well established. He spent, as a rule, the morning in hospital but was out of hospital for as much of the day as we would allow. He went for walks, sometimes in the snow, without fatigue. At end of November he contracted an upper respiratory infection with a rise in temperature of a degree or two, Fahrenheit. This infection subsided quite rapidly and required no treatment other than remaining indoors for two days. During the period of convalescence the anemia was in a large measure relieved. At time of admission the blood hemoglobin was 30 per cent.; on September 29, 30 per cent.; on October 27, 65 per cent.; on November 6, 80 per cent.

Weight and nutrition: On admission he weighed 107½ lb. When insulin treatment was started his weight was 116 lb. but the increase of 9 lb. is likely accounted for by the edema which increased during this period. On October 18, at the end of the first four weeks under insulin, his weight was 118½ lb. This represents probably a true increase of 11 lb., at least, since his edema subsided at the same time. During the subsequent period when no insulin was given, his weight fell to 109 lb. on November 1, but with treatment the weight had increased again to 115 lb. by November 8. On November 29, when he returned to hospital, his weight was 112 lb., gradually increasing to 118 lb. again at the time of his discharge. The weight, however, does not give a fair indication of the state of his nutrition. The muscles were hard and the general tissue turgor was much improved.

Carbohydrate metabolism: For the first five days in hospital he excreted from 55 to 95 gm. of glucose daily. This amount would be influenced by his diet preceding his admission to hospital. For the next six days his excretion varied from 32.2 to 47.5 gm. daily, an average of 41.3 gm. per day. During the preliminary period the basal metabolism was 1,009 calories; allowing additional 10 per cent. for digestion, etc., the caloric requirement would be about 1,100. The average amount of nitrogen in the urine during these six days was 6.96 gm., which is equivalent to 43 gm. of protein. Since 41 gm. of glucose was excreted, and 39 gm. of carbohydrate was given in the food, 104 gm. of fat would be required to make up the 1,100 calories. The total available glucose, therefore, was (carbohydrate plus 58 per cent. of the protein plus 10 per cent. of the fat) $39+0.58\times43+.1\times104$ gm. $=74.5$ gm. Average glucose utilized daily: 74.5 gm. -41.3 gm. $=33.2$ gm. From September 20 to October 18 the urine was sugar free with the exception of the first day and of September 28 and 29, when insulin of low potency was being given. The sugar excretion during the period October 19 to November 1, when the insulin administration was discontinued, is of interest. For two days no sugar was excreted; then daily amounts of 3.5 gm., 6.9 gm., 6.9 gm., 5.8 gm., 7.8 gm. That is to say that on the seventh day, with an intake containing over 70 gm. of available glucose, 7.8 gm. only was excreted. The developing ketosis and rising blood sugar, however, make it evident that the retained glucose was not all metabolized. For the next seven days, on a diet of protein 50 gm., fat 207 gm., carbohydrate 59 gm., the sugar excretion was much greater, with a maximum of 61.3 gm. on the sixth day and 48.7 gm. on the seventh day of the second week of no insulin treatment. The available glucose on this diet would be 108.7 gm. This indicates a utilization of 47 and 60 gm. of glucose on these two days, as compared with 33.2 gm. during the preliminary period. From November 2 to November 5 90 units of extract was given, and from the 6th to the 8th 60 units. The patient was practically free from glycosuria with the exception of the first day. For the next three weeks, while he was at his home, no further sugar appeared in the urine. During his second and third periods in hospital he continued to remain free of glycosuria with the exception of the night of January 3 and morning of January 4, when a small amount of sugar appeared as a result of giving no insulin for one day.

Polyuria: Insulin apparently has not brought about any change in the degree of the polyuria. During the preliminary period, with the exception of the first two days, the 24-hour output of urine varied from 3,150 c. c. to 5,700 c. c. After being free from glycosuria continuously for over two months, the urinary output varied from 3 to 5 litres. It would appear that the polyuria of some advanced cases of diabetes is not dependent entirely upon the glycosuria.

Nitrogen: As already stated, the nitrogen of the diet was not actually determined by analysis but was calculated from tables. However, from September 4 to October 25 (inclusive) the foodstuffs supplied were unchanged from day to day so that it may be assumed that the nitrogen intake was, at any rate, fairly constant for this period. During the last six days of the preliminary observation the urinary nitrogen varied between 6.3 gm. and 7.81 gm. with an average of 6.96 gm. While insulin was being given the urinary nitrogen was much less constant. From September 20 to October 18 the urinary nitrogen varied from 4.54 to 10 gm., the average being 5.93 gm. This would indicate that an average of 1.03 gm. of nitrogen was spared daily as a result of the insulin administered. From September 19 to September 25 no insulin was given and the diet remained unchanged. During these seven days the average urinary nitrogen was 7.13 gm. With the increased diets the nitrogen output is considerably increased.

Ketones. The characteristic relief of severe ketosis under insulin administration is seen on September 20 and again on November 3. Small amounts of acetone appeared in the urine from time to time while the injections were being given regularly. When the urine was collected at two-hour intervals it was found that the acetone was present only for an hour or two before the morning injection. It is likely that the glucose rendered available for combustion by insulin on the previous day had been completely utilized, and for a short time ketogenesis takes place. No doubt this would be avoidable by administering insulin and food late at night, but it is felt the danger of nocturnal hypoglycemia would outweigh any advantages so gained.

Blood sugar: The blood sugar estimations given in the table were made on samples of blood taken before breakfast, at a time when no food had been taken and no insulin given for fifteen hours. The estimation represents, as a rule, the high point in the 24 hours and indicates how successfully the blood sugar is being kept at a low level. These estimations were used to determine the adequacy of insulin dosage at a time when the potency of the extract was not being accurately assayed. A rise in the fasting blood sugar level on successive mornings would make it evident that the amount of insulin given was insufficient even in the absence of glycosuria. A fasting blood sugar rapidly falling on successive mornings indicates that the dosage is greater than the requirement. For this reason, on November 6 the dose was reduced from 90 units to 60 units. Again on November 12 insulin was increased from 20 units to 40 units a day, and on November 20 a further increase to 60 units. It is likely true that fasting blood sugars closer to normal are desirable, but

in this case this would necessitate division of the insulin into smaller and more frequent doses to avoid hypoglycemic reactions. It is noteworthy at any rate that a great deal of the clinical improvement occurred while this fasting blood sugar was above .16 per cent.

Several hypoglycemic reactions occurred in this patient. Most of these were mild and of short duration and, as a rule, no additional carbohydrate was furnished. From October 11 to October 18, while receiving 20 units three times a day at meal times (8 A. M., 12 M. and 5 P. M.) he had a slight reaction every night at 7 P. M. He complained of a feeling of nervousness and uncertainty. His blood sugars at this time varied between .068 per cent. and .078 per cent. A somewhat more severe reaction, with a profuse sweat, occurred on December 22 with a blood sugar of .65 per cent. and another on January 5 with a blood sugar of the same level. On January 7 a reaction occurred during which it was thought advisable to give 15 gm. of glucose. Below are given the blood sugar levels in a day on which a slight hypoglycemic reaction occurred. Meals were given at 8 a. m., 12 noon, and 5 p. m.; 20 units of insulin were given at the same hours.

8 a. m. . . .	.218 per cent. fasting level.
11 a. m. . . .	.143 per cent.
1 p. m. . . .	.234 per cent.
3 p. m. . . .	.102 per cent.
5 p. m. . . .	.080 per cent.
7 p. m. . . .	.078 per cent. reaction.

These may be compared with the blood sugar readings of October 19 (the first day when no insulin was given).

7 a. m. . . .	.122 per cent.
9 a. m. . . .	.166 per cent.
11 a. m. . . .	.300 per cent.
1 p. m. . . .	.205 per cent.
3 p. m. . . .	.198 per cent.
5 p. m. . . .	.214 per cent.
9 p. m. . . .	.202 per cent.

Subsequent history: He returned to his home on January 9. A letter from him, dated January 25, states that he is taking 13 units of insulin twice a day. His diet is 50 gm. protein, 150 of fat, 50 of carbohydrate. He had gained 5½ lb. since leaving hospital; that is to say his weight is now 123½ lb. He is in his office from 9.30 to 5 p. m., and states he has all the energy necessary for his work.

Remarks: This case is a typical example of the clinical improvement which may take place as a result of insulin treatment. There has apparently been almost complete restoration of mental and physical health, and a great deal of this improvement took place while the patient was on the same low diet which he had received before insulin treatment was given. The relief of glycosuria and ketosis is illustrated and the recurrence of these

two conditions when insulin treatment was discontinued. The influence of insulin in sparing nitrogen is shown, and it would appear that some increased power of carbohydrate utilization had occurred as a result of a month of insulin treatment.

J. W., widow, age 35, height 5 feet, weight 77 lb.; admitted November 4, 1922, discharged February 8, 1923.

Present illness: March, 1919, appetite became excessive, and troublesome pyorrhea developed; July, 1919, polyuria and polydipsia; September, 1919, burning micturition. At this time she began to feel weak and to lose weight. Sometime later a series of boils appeared in the perineal region. December, 1919, went to a sanitarium, where glycosuria was discovered and dietetic regulation started. January, 1920, while still in hospital, she was blind for several days; she had periods when she was very drowsy; she did not lose consciousness. When she left sanitarium the urine was sugar free on a diet of protein 100 gm., fat 130., carbohydrate 60 gm. During the summer of 1920 glycosuria recurred but cleared up on more careful dieting. October, 1920, menses stopped and she has not menstruated since. In April, 1921, re-entered hospital; blood sugar .2 per cent.; sugar in urine 6 per cent. Remained in hospital ten weeks on a low caloric diet, and on discharge she was allowed a diet of 600 calories. Weight was then 90 lb. as compared with 130 lb. before onset. Some edema was present. Fall of 1921, weakness became greater; she continued to lose weight. The polyuria was more marked; eye-sight became blurred; pruritus was present for two months. In February, 1922, she spent five more weeks in hospital and was rendered sugar free by a diet of 300 calories; sugar re-appeared in the urine when the diet was increased to 500 calories. This 500 calories was made up largely of protein. During spring of 1922 she was in a state of stupor for two days. This was followed by blurring of the eye-sight. May, 1922, had an attack of severe diarrhea and vomiting. In July the edema became much worse and was present from the waist downwards. There was some puffiness about the eyelids. She was becoming weaker and more nervous. On September 24 last she was admitted to the Johns Hopkins Hospital for twenty-eight days. An extract of the records was forwarded to us by the hospital. Dr. W. S. McCann has very kindly allowed us to include the results of his chemical investigation in this report (see Table II). It was noted then that she was extremely emaciated; weight 76½ lb.; basal metabolism 87 per cent. The diet given was, for part of the time, approximately 24 gm. of protein, 83 gm. of fat, and 33 gm. of carbohydrate. While on this diet she excreted from 18 to 41 gm. of glucose. When the diet was changed to 36 gm. protein, 77 gm. of fat and 29 gm. of carbohydrate, the glucose excretion was 44-48 gm. Six blood sugar estimations varied from .204 per cent. to .364 per cent. During her stay in hospital she received injections of insulin. This insulin was of low potency and had little, if any, effect upon the glycosuria. In the tables are given the diet and also the blood and urinary findings on the days when no insulin was administered. After discharge from hospital on October

21, 1922, she adhered fairly closely to diet of protein 24 gm., fat 80 gm., carbohydrate 33 gm. up to November 4 when she was admitted to the Toronto General Hospital.

Past illnesses: Frequent attacks of nasal infection; occasional sore throat; influenza, November, 1918, followed by bronchitis for two months.

Personal history: General health always good; married at the age of 27; normal weight was about 120 lb.; at time of onset of disease weight was 130 lb.; two children, normal confinements, no miscarriage; husband died in 1920.

Family history: Father dead—diabetes and apoplexy; paternal grandfather had diabetes; one paternal aunt had diabetes; one grandmother died of tuberculosis.

Examination: There was advanced emaciation of the muscles, although the edema of her face masked her thinness; there was also some edema of the feet and legs. Her weight on admission was 77 lb.; her true weight would be less than this figure on account of the edema present. Heavy acetone odor on the breath; skin dry and harsh. Digestive system—abdominal wall thin; peristalsis easily seen; edge of the liver palpable. Respiratory system—breath sounds rough; a few moist rales heard over both lungs. Cardio-vascular system—complained of shortness of breath on exertion; heart not enlarged; soft systolic murmur heard over the precordium, not influenced by position; radial arteries slightly thickened; blood pressure, systolic 85, diastolic 56. Nervous system—patient stated she was nervous; she had crying spells; frequently depressed; at times she was drowsy; knee jerks not obtained; muscle jerks of upper extremities obtained with difficulty; slight edema on the nasal side of the right optic disc.

Treatment: On admission she was ordered the diet which she had been taking—protein 24 gm., fat 80 gm., carbohydrate 33 gm. This diet was sufficient for her caloric requirement at the time, although there was a very considerable negative nitrogen balance. It served the purpose, however, of determining her power of glucose combustion. The metabolism in this case having been studied before admission, a preliminary observation was made for seven days only. Insulin was started on November 12, 20 units daily. The insulin given on the 12th and 13th was low in potency. On the 13th she obtained some extra food, which accounts for the increased glycosuria on that day. On November 14 a more potent preparation was administered, and on the 15th the amount was increased to three doses of 20 units each. On November 15 two hypoglycemic reactions occurred and 20 gm. additional carbohydrate was given. For this reason the dose of insulin was decreased on the 16th to 40 units for the day, and on the 17th to 20 units. On November 17, diet was increased to protein 30 gm., fat 95 gm., carbohydrate 40 gm. On the 19th 30 gm. additional carbohydrate was given. 20 units of insulin were given daily with this diet up to December 6, when the diet was changed to protein 60 gm., fat 100 gm., carbohydrate 60 gm., and the insulin was increased to 20 units twice daily. On December 8 the fat was increased to 150 gm. On De-

TABLE II

Patient J. W.

Extracts from John Hopkins Hospital Records. Sept. 29, 1922—Oct. 20, 1922

Date	Urine							Food Intake			
	Vol. cc.	R	Sp. G.	Sug. Gm.	Ketones SNP	Ketones FeCl3	Tot. Nit.	Prot.	Fat	CHO	Tot. Cal.
Sept.											
29	1700	....	....	13.9	P*	P*	6.9	25	87.5	35	1027
30	1750	....	....	21 8	P*	P*	9.1	25	87.5	35	1027
Oct.											
5	1450	....	....	23.2	P*	P*	6.3	25	87.5	35	1027
6	2030	....	....	18.8	P*	P*	8.5	25	87.5	35	1027
Oct.											
14	2450	....	....	39.2	P*	P*	7.4	24	83	33	975
15	2620	....	....	36.1	P*	P*	7.4	24	83	33	975
16	3500	....	....	25.5	P*	P*	8	24	83	33	975
17	3225	....	....	22.6	P*	P*	7.3	24	83	33	975
18	2775	....	....	47.1	P*	P*	9.2	36	77	29	953
19	3500	....	....	48.3	P*	P*	10.7	36	77	29	953
20	3600	....	....	44.6	P*	P*	10.4	36	77	29	953

*P denotes positive.

TABLE III

Mrs. J. W.

Age 35 Years. Height 5 Feet. Weight 77 Pounds.

Date	Urine								Fasting Blood Sug. %	Food Intake				Weight Lb.	Insulin	
	Vol. c.c.	R	Sp. G.	Sug. Gm.	Ketones SNP	Ketones FeCl3	Ketones Mg.	Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	cc.
4/11	2760	..	....	31.7	2*	1*	4498	....	....	24	80	33	948	77	.....	..
5/11	2275	H	1025	38	2	1	..	12.1	.320	24	80	33	....	....	.....	..
6/11	3260	H	1024	61	3	1	13299	15.0	....	24	80	33	....	....	.....	..
7/11	3570	H	1015	66.5	2	1	6112	12.43	.329	24	80	33	....	....	.....	..
8/11	3450	H	1020	49.5	2	1	9753	....	....	24	80	33	....	....	.....	..
9/11	4570	H	1012	73	2	1	9613	9.87	.26	24	80	33	....	79	.....	..
10/11	3570	H	1014	38.1	2	1	6423	10 09	....	24	80	33	....	79½	.....	..
11/11	3400	H	1015	48.5	2	1	3038	11.32	.284	24	80	33	....	80¾	.....	..

12/11	4150	H	1015	53.5	2	1	....	11.7	.282	24	80	33	....	....	9 a.m.	2
															5 p.m.	2
13/11	3400	H	1008	89.2	2	1	....	7.01	....	24	80	7	....	....	9 a.m.	2
															5 p.m.	2
14/11	5200	OH	1007	0	1	1	....	....	....	24	80	33	948	81	9 a.m.	2
															5 p.m.	2
15/11	4600	H	1006	0	0	0	....	7.04	....	24	80	53	1008	80	9 a.m.	2
															12 m.	2
															5 p.m.	2
16/11	5000	H	1007	0	0	0	....	....	....	24	80	33	948	79½	9 a.m.	1
															12 m.	1
															5 p.m.	1
17/11	4675	H	1005	0	0	0	....	8.20	....	30	95	40	1135	....	9 a.m.	1
															12 m.	1
															8 a.m.	1
18/11	3950	H	1005	0	0	0	....	....	.149	30	95	40	....	....	12 m.	1
															8 a.m.	1
19/11	....	..	....	....	..	..	....	....	.83	30	95	70	1225	....	12 m.	1
															8 a.m.	1
20/11	5100	H	1005	51.	1	1	....	....	....	30	95	40	1135	79¼	5 p.m.	1
															8 a.m.	1
21/11	4550	H	1006	0	0	0	....	....	.234	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
22/11	4950	H	1006	0	0	0	....	7.9	....	30	95	40	1135	81	5 p.m.	1
															8 a.m.	1
23/11	4400	H	1006	0	0	0	....	7.39	.272	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
24/11	4050	H	1009	0	0	0	....	6.9	....	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
25/11	4600	OH	1004	0	0	0	....	7.8	.100	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
26/11	4500	OH	1010	0	0	0	....	....	....	30	95	40	....	82¼	5 p.m.	1
															8 a.m.	1
27/11	4650	OH	1007	0	1	0	....	9.4	.154	30	95	40	....	82¼	5 p.m.	1
															8 a.m.	1
28/11	4500	OH	1007	0	0	0	....	7.6	....	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
29/11	4500	H	1008	0	0	0	....	9.9	.156	30	95	40	....	83¼	5 p.m.	1
															8 a.m.	1
30/11	4500	H	1007	0	0	0	....	12.6	....	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
1/12	4400	H	1007	0	0	0	....	6.6	.280	30	95	40	....	82½	5 p.m.	1
															8 a.m.	1
2/12	4850	H	1005	0	1	0	....	....	....	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
3/12	5250	H	1008	0	0	0	....	9 9	.280	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
4/12	4750	H	1005	0	0	0	....	7.1	....	30	95	40	....	83	5 p.m.	1

*Maximal intensity of sodium nitroprusside or ferric chloride reaction is indicated by 4.

TABLE III.—*Continued*

Date	Urine								Fasting Blood Sug. %	Food Intake				Weight Lb.	Insulin	
	Vol. cc.	R	Sp. G.	Sug. Gm.	Ketones		Ketones Mg.	Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	cc.
					SNP	FeCl3										
5/12	5350	H	1008	0	0	0	....	11.0	.245	30	95	40	....	....	8 a.m. 5 p.m.	1 1
6/12	5650	H	1006	0	0	0	....	11.3	....	60	100	60	1380	....	8 a.m. 5 p.m.	1 2
7/12	4750	H	1008	0	0	0	....	8.5	....	60	100	60	....	....	8 a.m. 5 p.m.	2 2
8/12	4050	H	1008	0	1	0	....	8.4	....	60	150	60	1830	....	8 a.m. 5 p.m.	2 2
9/12	4250	OH	1010	Tr.	0	0	....	....	....	60	150	60	....	82	8 a.m. 5 p.m.	2 2
10/12	4150	H	1008	0	0	0	....	8.6	.317	60	150	60	1830	82	8 a.m. 5 p.m.	2 2
11/12	4400	OH	1008	0	0	0	....	11.8	....	60	150	60	....	85	8 a.m. 5 p.m.	2 2
12/12	5100	OH	1009	0	0	0	....	9.2	.240	60	150	60	....	....	8 a.m. 5 p.m.	2 2
13/12	2650	OH	1010	0	0	0	....	10.8	....	60	150	60	....	84¼	8 a.m. 5 p.m.	2 2
14/12	4950	..	1007	0	1	0	....	10.9	....	60	150	60	....	....	8 a.m. 5 p.m.	2 2
15/12	4800	H	1006	Tr.	0	0	....	12	.287	60	150	60	....	....	8 a.m. 5 p.m.	2 2
16/12	4100	H	1010	1	0	0	....	10.2	....	60	150	60	....	....	8 a.m. 5 p.m.	2 2
17/12	4200	H	1010	2.1	0	0	....	11.7	....	60	150	60	....	....	8 a.m. 5 p.m.	2 2
18/12	4650	H	1008	Tr.	0	0	....	11.9	.350	60	150	60	....	85¼	8 a.m. 5 p.m.	2 2
19/12	4700	H	1010	0	0	0	....	12.8	....	60	150	60	....	....	8 a.m. 12 m. 5 p.m.	2 2 2
20/12	4250	H	1007	0	0	0	....	13.2	.225	60	150	60	....	82¾	8 a.m. 12 m. 5 p.m.	2 2 2
21/12	4200	H	1008	0	0	0	....	11.3	....	60	150	60	....	....	8 a.m. 12 m. 5 p.m.	2 2 2
22/12	....	..	....	...	..	..	....	....	.228	60	160	60	....	....	8 a.m. 12 m. 5 p.m.	2 2 2

1923																
4/1	1000	H	1006	0	0	0	....	....	....	30	95	40	1135	....	7 p.m.	1
															8 a.m.	1
5/1	4500	H	1007	0	0	0	....	11.7	.121	30	95	40	....	92	5 p.m.	1
															8 a.m.	1
6/1	4400	O11	1007	1.76	0	0	....	9.2	....	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
7/1	5000	H	1006	0	0	0	....	11.2	.264	30	95	40	....	....	5 p.m.	1
															8 a.m.	1
8/1	3300	H	1010	0	0	0	....	8.9	....	30	95	40	....	89	5 p.m.	1
															8 a.m.	2
9/1	3350	H	1013	0	0	0	....	7.3	.260	60	150	65	1830	90	5 p.m.	2
															8 a.m.	1
10/1	3850	H	1010	0	0	0	....	11.1	....	60	150	60	1810	....	12 m.	1
															5 p.m.	1
															8 a.m.	1
11/1	3250	H	1010	0	1	0	....	....	.220	80	200	80	2440	90	12 m.	1
															5 p.m.	1
															8 a.m.	1
12/1	4500	H	1009	0	0	0	....	12.6	....	80	200	80	....	....	12 m.	1
															5 p.m.	1
															8 a.m.	1
13/1	4250	H	1012	0	0	0	....	16.8	.231	80	200	80	....	90	12 m.	1
															5 p.m.	1
															8 a.m.	1
14/1	4500	H	1010	0	0	0	....	16.2	....	100	180	100	2420	....	12 m.	1
															5 p.m.	1
															8 a.m.	1
15/1	2400	H	1010	0	0	0	....	....	.221	100	180	100	....	91½	12 m.	1
															5 p.m.	1
															8 a.m.	1
16/1	4550	H	1010	0	0	0	....	11.1	....	100	180	110	2460	....	12 m.	1
															5 p.m.	1
17/1	4500	H	1010	15.5	0	0	....	....	.152	100	180	100	2420	....	8 a.m.	¾
															5 p.m.	¾
															8 a.m.	1
18/1	3455	H	1010	1.9	0	0	....	....	....	100	180	100	....	91¼	12 m.	1
															5 p.m.	1
															8 a.m.	1
19/1	4400	H	1010	0	0	0	....	....	.195	100	180	100	....	....	12 m.	1
20/1	4550	H	1015	102.8	0	0	....	14.3	.117	100	180	100	....	....	5 p.m.	1
21/1	4500	H	1015	124.2	1	0	....	....	.318	100	180	100	....	....	.. ..	..
22/1	4450	H	1020	264.3	2	0	1637.4	....	.337	100	180	100	....	....	.. ..	..
23/1	2400	H	1022	100 8	2	1	....	....	.347	100	180	100	....	....	.....	..
24/1	1570	H	1020	82.0	2	1	2227.3	....	....	100	180	100	....	88	.....	..
5/1	4550	H	1023	200.2	2	1	....	17.2	.416	100	180	100	....	....	.....	..
															8 a.m.	1
26/1	4100	H	1020	40 07	1	1	....	....	....	100	180	100	....	88	12 m.	1
															5 p.m.	1

TABLE III.—*Continued*

Date	Urine								Fasting Blood Sug. %	Food Intake				Weight Lb.	Insulin	
	Vol. c.c.	R	Sp. G.	Sug. Gm.	Ketones SNP	Ketones FeCl3	Ketones Mg.	Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	cc.
27/1	3600	..	....	40	2	1	....	....	.282	100	180	100	2420	....	8 a.m. 12 m. 5 p.m.	1 1 1
28/1	3500	H	1010	29.05	0	0	....	11.9	.364	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	1 1 1
29/1	2700	H	1015	16.45	0	0	....	....	.331	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	1 1 1
30/1	3300	H	1012	20.04	0	0	....	....	.309	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	1 1 1
31/1	3000	H	1015	30.7	0	0	....	....	.335	100	180	100	....	....	8 a.m. 12 m.	1 1
1/2	2200	H	1011	18.2	0	0	....	8 a.m. 11 a.m. 12 n. 1 p.m. 2 p.m. 3 p.m. 4 p.m. 5 p.m.	.356 .27 .217 .119 .200 .206 .185 .205	100	180	100	....	....	8 a.m. 5 p.m.	2 3
2/2	4600	H	1010	1.38	0	0	....	....	.267	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	3 3 3
3/2	1900	H	1010	0	0	0	....	....	.196	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	3 3 3
4/2	2250	..	1010	0	0	0	....	....	.104	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	3 3 3
5/2	4000	H	1010	0	1	0	....	....	....	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	3 3 3
6/2	2550	H	1015	0	0	0	....	....	.161	100	180	100	....	....	8 a.m. 12 m. 5 p.m.	3 3 3

cember 19 insulin was increased to 20 units three times a day on account of the low potency of this batch. On December 22 she went to her home for two weeks. During this time she estimated her diet as protein 30 gm., fat 95 gm., carbohydrate 40 gm., and she received 15 units of insulin twice a day. On her return to hospital on January 4 this diet was continued for five days. On January 9 it was increased to 60 gm. of protein, 150 gm. of fat, 60 gm. of carbohydrate, with an additional 5 gm. of carbohydrate on account of a reaction. On January 11 diet was increased to 80 gm. protein, 200 gm. fat and 80 gm. carbohydrate. On the 14th it was increased to 100 gm. of protein, 180 gm. fat, 100 gm. of carbohydrate. On January 17 she had a severe hypoglycemic reaction with a blood sugar of .033 per cent., and on January 17 the insulin was reduced to 8 units twice a day. On the 18th and 19th 10 units was again given three times a day. On January 20 the insulin was discontinued for six days without change of diet. On January 26 the insulin was continued, 10 units three times a day. On February 1 this was increased to 50 units and on February 2 to 90 units a day for four days, and then reduced to 70 units on February 6 and 40 units on the 7th and 8th. Cf. Table III.

General progress: Clinical improvement was remarkably rapid in this patient. During the seven days of preliminary observation she preferred to remain in bed on account of her weakness. Reading fatigued her. She was depressed and had occasional crying spells. Her edema was increasing. On November 14, the third day of insulin treatment, the first day of adequate dosage, she showed immediate relief of the many physical and mental symptoms associated with severe ketosis; she became more cheerful; her mental faculties became more acute, as shown, for example, by more accurate memory. Her visual acuity was better, and this, with increased powers of concentration, enabled her to read with enjoyment. The frequency of hypoglycemic reactions in the first few days of treatment necessitated an increase in the food intake on November 17. During the first week of treatment the edema disappeared. On November 19 she began to feel stronger. By this time she was sitting up or moving about the ward all day. She said she felt very hungry but no longer ravenous. By November 23 she was going out of doors for short walks and street car rides. Her increasing physical strength was in striking contrast with her emaciated musculature. Further progress continued without setback. By November 26 her weight was 82¼ lb., notwithstanding the disappearance of the edema. On December 11 her weight was 85 lb. For the next ten days there was practically no change in weight, probably as a result of her increasing activities. From December 22 to January 4 she was at her home in the Southern States. It is likely that during this time the diet was greater than estimated. On her return she weighed 92 lb. Up to January 19 her weight was practically constant. It could now be observed that the muscles were larger. It is interesting to note that the weight failed to increase in spite of a gradual increase in diet to over 2400 calories. This may be accounted for by the fact that a certain amount of her time was spent out of doors in winter, and that her physical exercise had been much increased. While

well contented with her diet of 100 gm. protein, 180 of fat, and 100 of carbohydrate, she was still hungry. It was not thought advisable to raise her diet still further. On January 20, when insulin was stopped for six days, sugar in large amounts reappeared in the urine. She stated that, during this time, she felt the cold more but did not observe much decrease in strength. On the fifth day she experienced some blurring of the sight but not on the sixth. On January 15 the systolic blood pressure was 104, diastolic 84, as compared with 86 and 56 at time of admission. The polyuria was not materially influenced by treatment. At the time of discharge, February 8, 1923, she looked well; her skin was soft and healthy in texture; she had a good color; the hair had a much better appearance, and she remarked that dandruff, which was abundant on admission, had now disappeared. She spent a good deal of her time out of the hospital; she did not complain of fatigue after her day's activities.

Carbohydrate metabolism: During the seven days preliminary observation the average daily excretion of sugar was 52.6 gm. The average urinary nitrogen was 11.8 gm., the equivalent of 73 gm. of protein. The basal metabolism was 87 per cent. Adding 10 per cent. to this for cost of digestion, the caloric requirement was approximately 950 calories. Since the carbohydrate excretion was greater than the carbohydrate of the food, the calories were supplied by the protein and fat so that it may be assumed that 80-90 gm. of fat was utilized. The total available glucose (the carbohydrate of the diet plus 58 per cent. of the protein plus 10 per cent. of the fat) would be equal to $33+0.58\times73+0.1\times90=84.6$ gm. Since 52.6 gm. of glucose was excreted, the total carbohydrate utilization was not more than 32 gm. This may be compared with the observations made at Johns Hopkins Hospital. On October 18, 19 and 20 the average daily nitrogen of the urine was 10.1, equalling 63 gm. of protein. The estimated available glucose would be $29+0.58\times63+0.1\times90=74.5$ gm. The average glucose excretion during this time was 46.6 gm. The glucose utilized was, therefore, 28.5 gm. From November 14 to January 19, with the exception of two or three days, the urine remained free of glucose. On January 20 insulin was discontinued to determine whether there had occurred any demonstrable change in the carbohydrate utilization power, and also to determine the carbohydrate equivalent of the insulin which was being administered. It is appreciated that only an approximation of these values is obtained by this means. From January 11 to January 19 she was maintained free of glycosuria on 30 units of insulin, except on January 17 when 15 units were given. Fasting blood sugars were considerably lower at the end of this period than at the beginning. It is evident, therefore, that 30 units of this batch contained more of the antidiabetic hormone than was required on this diet. The total glucose of the diet was (carbohydrate (100)$+0.58\times$ the protein (100)$+0.1\times$ the fat (180))$=176$ gm. Assuming a tolerance of 32 gm. of glucose, insulin would be required for 144 gm. of glucose. On January 20 the insulin administration was discontinued and for six days the glucose excretion was 102.8 gm., 124.2 gm., 264.3 gm., 100.8 gm., 82.0 gm., and 200.2 gm., an average of 145.7 gm. On January 20 the fasting blood sugar was .117 per cent., and on January 25 .416 per cent. So that, in addition to the

average daily excretion of 145.7 gm. of glucose, there was a very considerable amount of glucose accumulating in the blood and tissues during this period. These figures, as far as they go, do not demonstrate any increased power of carbohydrate utilization on the part of the patient, but, as is discussed later, comparisons of carbohydrate utilization when the patient is on a low diet with that obtaining when on a high diet must be accepted with caution. The amount of sugar excreted on these six days and the increase in the blood sugar level would indicate that the 30 units of this batch of insulin accounts for the combustion of more than 150 gm. of glucose. On January 26 the administration of 30 units of this batch of insulin was continued with an unexpected result. A glycosuria of 16 to 40 gm. of glucose occurred daily and the blood sugar levels remained high. The possibility of fatigue of the insular tissue, due to discontinuing the insulin while such a high diet was being given, appears to be a possible explanation of this result. On February 1 and 2 larger doses of a new batch were given. The urine became free of sugar on February 3 and the blood sugar levels continued to fall.

Nitrogen: During the preliminary period, six estimations of total urinary nitrogen were made. These varied from 9.87 to 15.0 gm. The average of these six determinations was 11.6 gm. On the first day of insulin treatment the total nitrogen in the urine was 11.70 gm.; on the second day, 7.01 gm.; on the fourth day, 7.04 gm.; on the sixth day 8.20 gm. On the 2nd and 4th day of insulin treatment, additional carbohydrate was given on account of hypoglycemia. On the 6th day the diet was increased somewhat in all foodstuffs. The sparing of nitrogen here is immediate and very material. This lowered nitrogen output, with four exceptions, continues up to December 5, while the patient received the diet of 30 gm. of protein, 95 gm. of fat, 40 gm. of carbohydrate. After this the protein in the food was increased to 60 gm. and nitrogen excretion was proportionately greater, although not averaging more than the original output when the patient was on the low diet of the preliminary period.

Ketosis: The relief of ketosis was not quite as rapid as is sometimes observed, because an extract of low potency was used for the first two days. As in other cases, traces of ketone appear in the urine from time to time while under insulin treatment.

Blood sugars and hypoglycemia: This patient was somewhat easily sent into a hypoglycemic reaction, and no effort was, therefore, made to keep the fasting blood sugar at a low level. Her kidney threshold was high and a fasting blood sugar over .3 per cent. did not result in glycosuria which could be detected in a 24 hour specimen. It was, therefore, possible to base the dose of insulin on this blood sugar level. Determination had to be done at frequent intervals because during much of the time of treatment preparations of insulin of unknown potency were used. Lower blood sugar levels would have been maintained had the potency of the extract been more accurately known. Many hypoglycemic reactions occurred while she was on the lower diets. The first reaction occurred at 12.15 a.m., November 15; when seen she had had several mild sweats and was feeling very nervous and excited; her blood

sugar was .052 per cent. After this the reactions were recognized more readily and she could, as a rule, detect their onset at .08 per cent. or even .085 per cent. They were rapidly relieved by small amounts of carbohydrate. On January 16 she had a somewhat more severe reaction at 8 p. m. with a blood sugar of .033 per cent. She had, for five days previously, received 30 units of the same batch daily without any such occurrences. The sudden appearance of hypoglycemia was unexpected. The reaction was of short duration and was readily relieved by 100 c.c. of orange juice. The cause of this reaction probably was some temporary gastro-intestinal upset which delayed the absorption of carbohydrate at the usual time.

Remarks: This patient, before coming under observation, had been treated without relief, under the most carefully controlled conditions, both by fasting and also by a diet calculated to cover the minimum caloric requirement, low in protein, low in carbohydrate and high in fat. During our own preliminary period while on a similar maintenance diet, the ketosis varying from 3 - 13 gm. of acetone bodies, the increasing edema, as well as her physical and mental condition, made manifest the gravity of her disease. In a very large measure insulin has brought about complete relief. As to the actual restoration of pancreatic power, it appears that the insular tissue has been injured beyond all possibility of even partial repair. Freedom from glycosuria from November 14 to January 19 has not resulted in any demonstrable increased power of carbohydrate combustion. During the early stage of treatment, while the patient was still on a low caloric diet, a very considerable sparing of nitrogen was brought about by insulin administration. The occurrence of hypoglycemia on January 16, at a time when she had been on a constant diet for several days and on insulin estimated as 30 units daily, but probably much stronger, illustrates the danger of high caloric diet under heavy insulin dosage. A supply of carbohydrate must be assured for each dose. It seems probable that any delay in the usual food assimilation will render the patient liable to hypoglycemia.

J. E., age 38, height 5 feet 7½ in., weight 111½ lb.; calculated basal caloric requirement 1512 calories; admitted November 25, 1922; discharged January 13, 1923.

Quite well two years ago. First noticed a rapid loss of weight; consulted a physician and glycosuria was detected. Appetite has been excessive for the past two years but thirst has never been troublesome. He was placed on a restricted diet but it was insufficient for him to do work and he has only been aglycosuric at intervals. At first he could get sugar free by one day's starvation but for the past two months has not been able to get sugar free by several days' starvation. Lately he has

noticed increasing weakness so that it was very difficult to climb stairs.

Past illnesses: Typhoid fever as a child; influenza in 1918.

Family history: One child died in diabetic coma; brother's two children died of diabetes.

Examination: General—well developed; poorly nourished; skin dry and loose; teeth fair; glands normal; tongue clean; thyroid normal; fundi normal; membrana tympani normal. Circulation—radials definitely sclerosed; pulse 84, good volume; B.P. 98/56; heart normal. Respiratory system—chest well formed; expansion free, synchronous and symmetrical; percussion note impaired at bases; coarse rales at bases; evidence of chest pathology cleared up soon after admission to hospital. Digestive system—liver and spleen not palpable; nothing abnormal found. Nervous system—intelligent; sensation normal; co-ordination good; cranial nerves show no lesion; reflexes present and normal except knee jerks which are obtained only on reinforcement.

The accompanying table (Table IV) indicates the results obtained by dietetic measures alone as contrasted with dietetic measures plus insulin therapy. On a basal diet the urinary glucose averaged well over 50 gm. a day. Acetone bodies in urine exceeded 12 gm. daily but fell to half that amount. The blood sugar was .372 per cent. but decreased to .289 per cent. under dietetic measures alone. The required amount of insulin to make him sugar free was calculated and given on December 6, 1922. He was practically sugar free on December 7, 1922, and acetone bodies rapidly decreased. The blood sugar fell during the day to .162 per cent. He was sugar free and practically free from ketosis for the following 36 days before discharge from hospital, though the insulin given was cut to one-third the original dose and the diet gradually raised to 2250 calories. The fasting blood sugar in the last three weeks was not higher than .126 per cent.

This case illustrates several points of interest: First, when the blood sugar is high, and consequently there is a larger amount of tissue sugar, a larger amount of insulin is required to make the patient aglycosuric than is necessary to maintain him in this condition. It will be noticed that after the first four days the insulin was reduced from 60 units to 40 units, while the total glucose intake remains the same. It is possible that the amount of acetone bodies present in the body also caused a certain amount of insulin to be used up in their destruction. Another point is an apparent increase in the carbohydrate tolerance of the patient under insulin. From December 31 to January 12 inclusive, this patient was on the same dose of the same preparation of insulin. During that time the diet was raised 550 calories and 23 gm. total glucose. It will be noted that the patient maintained approximately the same blood sugar level during this period and acetone bodies were negligible in amount. Such cases as these introduce a source of fallacy in determining the carbohydrate

TABLE IV

Patient J. E.

Age 38 years. Height 5 feet, 7½ inches. Weight 111½ pounds. Surf. area 1.59 sq. m.

Date	Urine								Blood Sugar %	Food Intake					Weight Lb.	Insulin	
	Vol. c. c.	R	Sp.G.	Sug. Gm.	Ketones			Tot. Nit.		Prot.	Fat	CHO	Total Glucose Gm.	Tot. Cal.		Time	c.c.
					SNP	FeCl3	Mg.										
1922																	
25/11	.....	..	..	+3	2	1	.....	.....	.....	38	126	37	72	1434	111½	.....	..
26/11	2400	H	20	62.4	2	1	3880	11.04	.....	38	126	37	72	1434	.....	.....	..
27/11	2480	H	15	52.08	1	1	3706	9.9	.372	34	134	39	73	1508	.....	.....	..
28/11	2400	H	18	46.6	2	2	8117.2	9.91	.275	34	134	39	73	1508	114¾	.....	..
29/11	4400	H	20	52.68	2	1	12232	12.7	.....	34	134	39	73	1508	.....	.....	..
30/11	3750	H	17	58.5	2	1	11091.2	.....	.....	34	134	39	73	1508	.....	.....	..
1/12	4210	H	17	66.5	2	1	7346	13.8	.306	34	134	39	73	1508	113	.....	..
2/12	2950	H	20	63.7	2	1	.....	11.3	.....	34	134	39	73	1508	.....	.....	..
3/12	3000	H	20	47.4	2	1	.....	11.7	.....	34	134	39	73	1508	.....	.....	..
4/12	3350	H	20	52.9	2	1	.....	13.	.289	34	134	39	73	1508	.....	.....	..
5/12	2950	H	15	37.1	2	1	6262	10.3	.....	34	134	39	73	1508	.....	.....	..
12-6	250	H	10	.89	1	0	.....	.....	.....	..	...	..	..	....	.....	8 a. m.	2
6-6	.....	..	.....	.....	..	..	.....	.....	.....	..	...	..	..	....	.....	4 p. m.	2
6-12	2050	H	11	15.3	1	0	4510	10.5	.162	34	134	39	73	1508	114½	12 m.	2
6-12	250	H	10	0.275	2	1	.....	.....	.....	..	...	..	..	....	.....	8 a. m.	2
12-6	600	H	10	0	1	0	.....	.....	.....	..	...	..	..	....	.....	4 p. m.	2
6-6	2300	H	10	0.23	1	0	2110	4.8	.....	34	134	39	73	1508	.....	12 m.	2
6-12	200	H	06	0	1	0	.....	.....	.....	..	...	..	..	....	.....	8 a. m.	2
12-6	750	H	06	0	1	0	.....	.....	.....	..	...	..	..	....	.....	4 p. m.	2
6-6	1750	H	06	0	1	0	.....	9.7	.....	34	134	39	73	1508	117¼	12 m.	2
6-12	680	H	11	0	1	0	.....	.....	.....	..	...	..	..	....	.....	8 a. m.	2
12-6	200	H	15	0	2	0	.....	.....	.....	..	...	..	..	....	.....	4 p. m.	2
6-6	2825	H	10	0	1	0	.....	3.7	.076	34	134	39	73	1508	.....	12 m.	2
																8 a. m.	2
10/12	2460	H	11	0	17	0	.....	6.6	.139	34	134	39	73	1508	.....	4 p. m.	2
																8 a. m.	2
11/12	3400	H	10	0	0	0	.....	3.4	.....	34	134	39	73	1508	.....	4 p. m.	2
																8 a. m.	2
12/12	4100	H	10	0	1	0	652	6.55	.149	34	134	39	73	1508	.....	4 p. m.	2
																8 a. m.	2
13/12	4500	H	08	0	17	0	.....	6.7	.....	31	134	39	73	1508	119	5 p. m.	2
																8 a. m.	2
14/12	2700	..	10	0	17	0	.....	5.4	.....	34	134	39	73	1508	.....	5 p. m.	2
																8 a. m.	2
15/12	3800	H	09	0	0	0	.....	8.3	.....	34	134	39	73	1508	.....	5 p. m.	1
																8 a. m.	2
16/12	2900	H	11	0	0	0	.....	7.2	.136	34	134	39	73	1508	.....	5 p. m.	1
																8 a. m.	2
17/12	4500	H	10	0	0	0	.....	9 9	.....	34	134	39	73	1508	.....	5 p. m.	2
																8 a. m.	2
18/12	4050	H	10	0	0	0	.....	10.5	.152	34	134	39	73	1508	.....	5 0. m.	2

19/12	4500	H	07	0	17	0	.....	7.6	....	34	134	39	73	1508	.....	8 a. m.	2
																5 p. m.	2
20/12	3550	H	07	0	0	0	.....	.....	.097	34	134	39	73	1508	117	8 a. m.	2
																5 p. m.	2
21/12	3600	H	10	0	0	0	.....	6.8	....	34	134	39	73	1508	118	8 a. m.	2
																5 p. m.	2
22/12	4150	..	08	0	17	0	.....	8.0	.115	34	134	39	73	1508	118¼	8 a. m.	2
																5 p. m.	1½
23/12	2725	H	10	0	0	0	.....	4 1	....	34	154	44	80	1708	.....	8 a. m.	1
																5 p. m.	1
24/12		LOST							.125	34	154	44	80	1708	118½	8 a. m.	1
																5 p. m.	1
25/12	1600	OH	12	0	17	0	.....	7.5	....	34	154	44	80	1708	.....	8 a. m.	1
																5 p. m.	1
26/12	2250	H	10	0	0	0	.....	8.1	.116	34	154	44	80	1708	122	8 a. m.	1
																5 p. m.	1
27/12	1800	H	15	0	1	0	.....	6.8	....	34	154	44	80	1708	121½	8 a. m.	1
																5 p. m.	1
28/12	3350	H	10	0	1	0	.....	10.05	.126	34	154	44	80	1708	.....	8 a. m.	1
																5 p. m.	1
29/12	3050	H	10	0	1	0	.....	7.6	....	34	154	44	80	1708	122	8 a. m.	1
																5 p. m.	1
30/12	3300	H	11	0	17	0	.....	8.1	....	34	154	44	80	1708	121½	8 a. m.	1
																5 p. m.	1
31/12	4150	H	10	0	0	0	.....	9.4	.123	34	154	44	80	1708	121½	8 a. m.	1
1923																5 p. m.	1
1/1	1800	H	15	0	1	0	.....	6.8	....	34	154	44	80	1708	.....	8 a. m.	1
																5 p. m.	1
2/1	2300	H	12	0	1	0	.....	6.4	.119	34	154	44	80	1708	.....	8 a. m.	1
																5 p. m.	1
3/1	3000	H	10	0	1	0	.....	8.1	....	37	174	49	89	1910	.....	8 a. m.	1
																5 p. m.	1
4/1	3100	H	07	0	0	0	.....	....	.115	37	174	49	89	1910	122	8 a. m.	1
																5 p. m.	1
5/1	3400	H	10	0	1	0	.....	7.8	....	37	174	49	89	1910	.....	8 a. m.	1
																5 p. m.	1
6/1	3100	H	17	0	0	0	.....	6.8	.118	37	174	49	89	1910	.....	8 a. m.	1
																5 p. m.	1
7/1	3650	H	10	0	1	0	.....	.....	....	45	184	49	94	2032	121½	8 a. m.	1
																5 p. m.	1
8/1	2500	H	13	0	1	0	.....	.....	.115	45	184	49	94	2032	.....	8 a. m.	1
																5 p. m.	1
9/1	2750	H	13	0	1	0	.....	7.7	....	45	184	49	94	2032	.....	8 a. m.	1
																5 p. m.	1
10/1	2800	H	10	0	17	0	.....	7.3	.120	45	184	49	94	2032	.....	8 a. m.	1
																5 p. m.	1
11/1	4250	H	10	0	1	0	.....	10.6	....	45	184	49	94	2032	121	8 a. m.	1
																5 p. m.	1
12/1	....	..	..	.....	..	..	.....	7 4	....	53	194	49	100	2254	.....	8 a. m.	1
13/1	....	..	..	.....	..	..	.....	.....	....	53	194	49	100	2254	.....	Discharged 10 a. m.	

equivalent of insulin. Calculating the carbohydrate equivalent of the insulin used on December 11, we find it is somewhat less than 13 gm. carbohydrate per c.c. since the blood sugar was rising at this time. By a similar calculation the carbohydrate equivalent of the last insulin might be 40 gm. or 30 gm. according to whether the last or first diet was used in making the calculation, or even 26 gm. per c.c. if one were disposed to attribute the increased tolerance exhibited on December 31 over that of December 11 as due to the patient's own recovery. The conservation of nitrogen when glucose is being burned is also shown in this case.

W. I., age 57, height 5 feet 9 in., weight 106 lb.; calculated basal caloric requirement 1420 calories; admitted to hospital October 14, 1922; discharged November 25, 1922.

A thin emaciated man in moderate state of acidosis; deep breathing; odor of acetone on breath; entered hospital complaining of weakness, sleepiness, and loss of vision for past three weeks. Two years ago consulted a physician for a pain in the back, and sugar was found in the urine. A diet of sorts was prescribed but patient was only occasionally sugar free, and gradually went down the hill. Best weight, two years ago, 145 lb.; six months ago, 128 lb.

Family history: Daughter died of diabetes a few weeks ago; one son has diabetes.

Examination: General—poorly nourished; skin dry; atrophic; teeth absent; tonsils normal; odor of acetone on breath. Circulatory system—distinctly palpable vessels; otherwise good. Respiratory system—breathing prolonged; otherwise normal. Digestive system—teeth removed. Complains of regurgitation of gas and feeling of heaviness in epigastrium. Colon spastic; right inguinal hernia present. Nervous system—intelligent; reflexes normal; has dimness of vision and slight deafness of left ear. Retina shows increased tortuosity of the blood vessels. Cf. Table V.

Average excretion of sugar during preliminary period of observation, 38 gm. per day on a diet of: protein 33 gm., fat 125 gm., carbohydrate 36.6 gm.; calories 1411. Blood sugar 0.250 per cent. On October 24 he was given 40 units of insulin, calculated to make him sugar free, which it did. With a similar dose of a new batch of insulin he excreted an average of 10 gm. of sugar, and the dose was increased to 50 units to make him sugar free. On this dose the fasting blood sugar fell steadily to .138 per cent. on November 4, and at 10 p. m. that night to .075 per cent., when a slight feeling of tremulousness was noted. The dose was then reduced 20 per cent., and the blood sugar rose to .145 per cent., though he still remained sugar and ketone free. At this point an extract which had suddenly deteriorated in potency was employed, with immediate rise in the fasting blood sugar, and excretion of 5 gm. of sugar per day for 3 days. As the next batch of insulin used caused a slight reaction requiring 50 c.c. of orange juice to control it, the diet was increased to: protein 33 gm., fat 141 gm., carbohydrate 41.6 gm.; calories 1566, on November 16, and again on November 20 to: protein 33 gm., fat 161 gm., carbohydrate

46.6 gm., calories 1766, as he had a reaction with sweating and tremulousness at 10.30 p.m. the night before, during which the blood sugar was .058 per cent., and the dose was reduced to 30 units. On increasing to 40 units a reaction took place at midnight, in which the patient became flushed, started perspiring, then muttering incoherently, then became unconscious, during which time his blood sugar was .041 per cent., pulse 62 (reduced 16 beats per minute as we have noted in other severe reactions). 1 c.c. epinephrin 1/1000 was given and patient recovered sufficiently to swallow 100 c.c. orange juice and 15 gm. glucose. Complete recovery was extraordinarily prompt (3-5 minutes).

The patient was discharged on a diet of—protein 33 gm., fat 181 gm., carbohydrate 51.6 gm., calories 1967, using 15 units of insulin per day. His weight had increased steadily to 119 lb.—a gain of 13 lb. During the past two months he has been living at home on the diet prescribed. He has had a feeling of tremulousness once, which passed off with the next meal. He has been continuously sugar free except on three days, when he attempted to reduce the dose of insulin to 10 units per day. After the first few days of insulin treatment the amblyopia, which was unassociated with any visible eye ground changes, began to disappear. Coincidently his weakness gradually disappeared; he lost his slouch; and his morose, cranky, despondent disposition altered, and he became cheerful and happy. He is now back at his former occupation, which he finds easy. His eyesight is good but he has not altered in weight since discharge from hospital.

R. B., age 18, height 5 feet 8 inches, weight 114 lb.; calculated basal caloric requirement 1574 calories; admitted December, 1922; discharged January 16, 1923.

Three years ago patient noticed onset of great thirst and polyuria. On consulting a physician the diagnosis of diabetes was made and he was given a diet of meat, oatmeal and 5 and 10 per cent. vegetables. On this he was sugar free part of the time but became careless. A dietetic regime was carefully worked out for him a year ago and he was aglycosuric for a considerable period. Latterly he has not adhered to his diet and has had more or less sugar continuously.

Past illnesses: Measles in childhood.

Family history: Negative for diabetes.

Examination: Aside from his languid manner and feeling of weakness, several carious teeth, and enlarged cervical lymphatic glands and evidence of loss of weight, there was nothing abnormal found on physical examination.

The accompanying table (Table VI) summarizes the results of treatment in this case. It will be noted that on admission there was a considerable excretion of sugar and acetone bodies which gradually decreased on the basal diet to approximately 20 gm. of glucose per day, and 3 gm. of acetone bodies. The use of a non-nutrient diet for one day did not permanently decrease the glucose excretion but the blood sugar and acetone bodies decreased. The use of insulin promptly made him aglycosuric. The acetone bodies disappeared less rapidly. The blood sugar level fell quite rapidly and, keeping the dose of insulin the same, it was possible to

TABLE V

Patient W. I.

Age 57 Years. Height 5 Feet, 9 Inches. Weight 106 Pounds. Surf. Area 1.56 Sq. M.

Date	Urine								Blood Sugar %	Food Intake				Tot. Cal.	Wt. lb.	Insulin	
	Vol. cc.	R	Sp. G.	Sug. Gm.	Ketones			Tot. Nit.		Prot.	Fat	CHO	Total Glucose			Time	cc.
					SNP	FeCl3	Mg.										
1922																	
14/10	....	H	25	....	2	1	.....	.....	....	38	119	33	67	1355	106	.....	...
15/10	1400	H	25	2	2	1	.....	....	....	38	119	33	67	1355	.....	.....	...
16/10	2270	H	16	38	3	2	14591	10.7	....	33	125.9	36.6	69	1411	105¾	.....	...
17/10	3850	H	14	42.7	3	2	19735	13.47	....	33	125.9	36.6	69	1411	.....	.....	...
18/10	3000	H	16	19	3	2	14709	8.82	....	33	125.9	36.6	69	1411	.....	.....	...
19/10	2450	H	16	26.5	3	2	11684	11.13	....	33	125.9	36.6	69	1411	.....	.....	...
20/10	4000	H	14	40	3	2	11952	10.64	....	33	125.9	36.6	69	1411	.....	.....	...
21/10	3550	H	20	37.8	3	1	.....	11.6	.250	33	125.9	36.6	69	1411	110	.....	...
22/10	3850	H	13	45.5	1	1	.....	8.85	....	33	125.9	36.6	69	1411	.....	.....	...
23/10	2550	H	15	29.88	3	1	.....	6.9	.246	33	125.9	36.6	69	1411	.....	.....	2
																1 p. m.	2
24/10	2850	H	03	0	3	0	459	3.9	..	33	125.9	36.6	69	1411	111½	6 p. m.	2
																1 p. m.	2
25/10	3750	H	06	8.2	3	1	1560	7.5	.163	33	125.9	36.6	69	1411	..	6 p. m.	2
																1 p. m.	2
26/10	3500	H	07	12.5	1	0	2457	7.3	...	33	125.9	36.6	69	1411	113½	6 p. m.	2
																1 p. m.	2
27/10	4000	H	07	8.7	1	0	792	6.0	.194	33	125.9	36.6	69	1411	115¼	6 p. m.	2
																1 p. m.	2½
28/10	4150	H	06	4.3	1	0	1360	7.4	.161	33	125.9	36.6	69	1411	.. ..	6 p. m.	2½
7-2	1400	H	08	4.9	3	0											
2-6	1500	H	05	0	1	0	.....	.....	....	33	125.9	36.6	69	1411	.. ..	.....	...
6-10	1350	H	05	0	0	0											
10-7	1000	H	07	0	2	0	.....	.....	....	....	....	....	....	....	....	1 p. m.	2½
29/10	....	..	..	..	..	..	900	7.8	....	33	125.9	36.6	69	1411	.....	6 p. m.	2½
7-12	375	H	10	+	3	1											
12-4	1250	OH	08	3.8	1	0	.....	..	....	33	125.9	36.6	69	1411	....	.....	...
4-8	850	H	08	1	0	0											
8-7	1900	OH	06	0	2	0			....	....	....	....	....	....	....	1 p. m.	2½
30/10	....	....	....	....	....	..	768	4.8	....	33	125.9	36.9	69	1411	.....	6 p. m.	2½
																1 p. m.	2½
31/10	4900	H	06	0	0	0	.....	11.3	.132	33	125.9	36.6	69	1411	.....	6 p. m.	2½
																8 a. m.	2½
1/11	4500	H	05	0	1	0	634	7.71	....	33	125.9	36.6	69	1411	117	3 p. m.	2½
									8 a. m. .162								
																8 a. m.	2½
2/11	3250	H	08	0	1	0	282	....	3 p. m. .143	33	125.9	36.6	69	1411	.....	6 p. m.	2½

3/11	3750	II	10	0	1	0	.	7.07	....	33	125.9	36.6	69	1411	113½	8 a. m.	2½
									8 p. m. .138							6 p. m.	2½
									10 p. m.							8 a. m.	2½
4/11	4500	II	05	0	1	0	265	7.86	.075	33	125.9	36.6	69	1411	116½	6 p. m.	2½
5/11	4400	II	08	0	0	0	. .	7.23	. . .	33	125.9	36.6	69	1411	114½	8 a. m.	2¼
																5 p. m.	2
6/11	4500	II	07	0	1	0	468	12.1	.113	33	125.9	36.6	69	1411	. . . .	8 p. m.	2
																6 p. m.	2
7/11	4250	II	09	0	1	0	1508	.	.	33	125.9	36.6	69	1411	113¾	8 a. m.	2
																6 p. m.	2
8/11	4250	II	10	0	1	0	85	6.25	.115	33	125.9	36.6	69	1411	116	8 a. m.	2
																6 p. m.	2
9/11	2500	II	10	0	1	0	404	3.85	.	33	125.9	36.6	69	1411	116¼	8 a. m.	2
																6 p. m.	2
10/11	4500	II	08	0	0	0	.	5.1	.095	33	125.9	36.6	69	1411	113	8 a. m.	2
																6 p. m.	2
11/11	3250	OII	10	3.0	1	0		6.35	.	33	125.9	36.6	69	1411	113	8 a. m.	2
																6 p. m.	2
12/11	3750	II	11	5.3	1	0	.	6.30	.189	33	125.9	36.6	69	1411	. .	8 a. m.	2
																6 p. m.	2
13/11	2450	II	10	5.7	1	0	. .	12.95	.	33	125.9	36.6	69	1411	.	8 a. m.	2
																6 p. m.	2
14/11	2250	II	10	0	0	0	. .	4.56	.124	33	125.9	36.6	74	1432	110¾	8 a. m.	2
																6 p. m.	2
15/11	2500	II	11	0	0	0		4.75	.	33	125.9	36.6	69	1411	113½	8 a. m.	3
																6 p. m.	1
16/11	4500	II	07	0	1	0		7.25	.135	33	140.9	46.6	75.5	1566	116¼	8 p. m.	2
																6 p. m.	2
17/11	2350	II	11	0	0	0		4.70	....	33	140.9	46.6	75.5	1566	.	8 a. m.	2
																6 p. m.	2
18/11	2800	II	12	0	0	0		13.7	....	33	140.9	46.6	75.5	1566	115¾	8 a. m.	2
									10.30							6 p. m.	2
									p. m.								
19/11	2950	II	10	0	0	1		1 86	.041	33	140.9	51.6	80.5	1586	.	8 a. m.	2
																6 p. m.	1
20/11	4050	II	10	0	0	0	.	10.09	....	33	160.9	51.6	82.5	1766	119¼	8 p. m.	2
																6 p. m.	1
																8 a. m.	2
21/11	4050	II	10	0	0	0		5.8	.	33	160.9	51.6	82.5	1786	.	4 p. m.	1
									2 10 a m.							12 m.	1
									8 a. m.								
22/11	5150	OII	11	11.6	1		2193	5.7	.170	33	180.9	76	107.5	1986		. ....	.
23/11	4900	II	10	0	0	0	.	. .	.	33	180.9	51.6	89 5	1886	. .	8 a. m.	1
																6 p. m.	½
24/11	2350	II	08	0	1	0	.	.	.192	33	180.9	51.6		1886	.	8 a. m.	1
																5 p. m.	½
25/11	. .	.						. .	....	33	180.9	51.6		1886	.	8 a. m.	1
																5 p. m.	½
																Discharged	

TABLE VI

Patient R. B.

Age 18 Years. Height 5 Feet, 8 Inches. Weight 114 Pounds. Surf. Area 1.6 sq. m.

Date	Urine				Ketones			Tot. Nit.	Blood Sugar %	Food Intake					Weight lb.	Insulin	
	Vol. cc.	R	Sp.G	Sug. Gm.	SNP	Fe Cl3	Mg.			Prot.	Fat	CHO	Total Glucose	Tot. Cal.		Time	cc.
6 a. m.																	
9 p. m.																	
1/12	1700	H	16	93.5	2	1	....	.....	....	38	126	37	72	1434	114	.....	..
2/12	2460	H	28	71.7	2	2	....	8	.302	38	126	37	72	1434	.....	.....	..
3/12	2150	H	20	40.8	2	1	....	11.3	....	35	140	41	76	1564	.....	.....	..
4/12	1950	H	18	38.27	2	1	....	8.4	....	35	140	41	76	1564	.....	.....	..
5/12	2650	H	18	27.6	2	1	6021	11.3	.251	35	140	41	76	1564	.....	.....	..
6/12	2650	H	18	18.9	2	1	5191	7.9	....	35	140	41	76	1564	.....	.....	..
7/12	3050	H	09	14.5	tr.	0	1098	.....	.253	Non	nutrients				117¾	.....	..
8/12	2650	H	12	21.3	2	1	6439	.....	....	35	140	41	76	1564	.....	.....	..
9/12	3250	H	15	31.2	2	1	....	8.7	.229	35	140	41	76	1564	.....	.....	..
10/12	2800	H	15	14.7	2	1	....	6.1	....	35	140	41	76	1564	.....	.....	..
11/12	3800	H	13	21.9	2	1	920	6.7	.245	35	140	41	76	1564	.....	.....	..
12/12	3850	H	11	25.2	2	2	2722	4.9	....	35	140	41	76	1564	.....	.....	..
13/12	2500	H	12	20.1	2	1	1180	8.	.182	35	140	41	76	1564	.....	.....	..
14/12	2500	H	13	16.5	2	0	1197	2	....	35	140	41	76	1564	.....	.....	..
6-8 a. m.	280	H	08	0	1	0	....	.....	.172	..	..	..	..	....	.....	.....	
8-10 a. m.	230	H	11	0.64	2	1?	....	.....	.150	..	..	..	..	....	.....	.....	..
10-12 a. m.	380	H	07	0	2	0	....	.....	.182	35	140	41	76	1564	.....	8 a. m.	1
12-2 p. m.	580	H	08	0	1	0	....	.....	....	..	..	..	..	....	.....	.....	..
2-4 p. m.	400	H	12	0	2	0	....	.....	.193	..	..	..	..	....	.....	.....	..
4-6 p. m.	250	H	13	0	1	0	....	.....	.235	..	..	..	..	....	.....	.....	..
6-6 p. m.	1700	H	08	0	1	0	4001	4.55	.157	35	140	41	76	1564	.....	5 p. m.	1
6-12	400	OH	15	0.2	2	0	....	.....	....	..	..	..	..	....	.....	.....	
12-6	1950	H	13	3.04	2	0	....	.....	....	..	..	..	..	....	.....	8 a. m.	1
6-6	1800	H	07	0	1	0	991	5.8	....	35	140	41	76	1564	.....	5 p. m.	1
																8 a. m.	1
17/12	2750	H	10	0	1	0	403	6.05	....	35	140	41	76	1564	.....	5 p. m.	1
																8 a. m.	1
18/12	2450	H	15	0	2	0	953	7.4	.157	35	140	41	76	1564	.....	5 p. m.	1
																8 a. m.	1
19/12	2300	H	10	0	2	0	442	.....	....	35	140	41	76	1564	.....	5 p. m.	1
																8 a. m.	1
20/12	2250	H	09	0	2	1	....	.....	.134	35	140	41	76	1564	117¾	5 p. m.	1
																8 a. m.	1
21/12	3450	H	12	0	1	1	....	8.97	....	35	140	41	76	1564	118	5 p. m.	1
																8 a. m.	1
22/12	3250	.	12	0	1	0	....	7.8	.139	35	140	41	76	1564	117½	5 p. m.	1

23/12	2750	II	12	0	0	0	..	6.6		35	140	41	76	1564	118	8 a. m. 5 p. m.	1 1
24/12	LOST								.111	35	140	41	76	1564	.....	8 a. m. 5 p. m.	1 1
25/12	2200	II	11	0	0	0	..	5.7	.	35	140	41	76	1564	117½	8 a. m. 5 p. m.	1 1
26/12	1800	II	10	0	1	0	..	4.8	.121	35	160	46	83	1764	.....	8 a. m. 5 p. m.	1 1
27/12	2700	II	10	0	2	1	.	.....	....	35	160	46	83	1764	....	8 a. m. 5 p. m.	1 1
28/12	2300	II	12	0	1	0	...	.....	.131	35	160	46	83	1764	.....	8 a. m. 5 p. m.	1 1
29/12	2450	OII	10	0	1	0	...	8.1	...	35	160	46	83	1764	.....	8 a. m. 5 p. m.	1 1
30/12	2500	II	10	0	1	0	..	.....	....	35	160	46	83	1764	. ....	8 a. m. 5 p. m.	1 1
31/12	2700	H	10	0	0	0	..	.....	.171	35	160	46	83	1764	.....	8 a. m. 5 p. m.	1 1
1923 1/1	2500	II	12	0	1	0	...	13.4	...	35	160	46	83	1764	....	8 a. m. 5 p. m.	1 1
2/1	2300	II	10	0	1?	0	....	.....	.145	35	160	46	83	1764	188	8 a. m. 5 p. m.	1 1
3/1	2200	II	11	0	1	0	...	.....	.	35	160	46	83	1764	....	8 a. m. 5 p. m.	1 1
4/1	2000	II	12	0	+?	0	....	.....	.135	35	160	46	83	1764	.....	8 a. m. 5 p. m.	1 1
5/1	1800	II	11	0	1	0	...	.....	...	35	160	46	83	1764	118½	8 a. m. 5 p. m.	1 1
6/1	2500	H	08	0	0	0	...	.....	.112	35	160	46	83	1764	....	8 a. m. 5 p. m.	1 1
7/1	1900	H	14	0	1	0	....	.....	...	35	180	51	90	1914	118¼	8 a. m. 5 p. m.	1 1
8/1	1800	II	13	0	1	0	.	.....	.138	35	180	51	90	1914	.....	8 a. m. 5 p. m.	1 1
9/1	2250	H	20	0	1	0	....	.....	....	35	180	51	90	1941	.....	8 a. m. 5 p. m.	1 1
10/1	....	II	10	0	1?	0	..	. .	.095 12.05 p. m. .056 12.35 p. m.	35	180	51	90	1944	. .	8 a. m. 5 p. m. 8 a. m.	1 1 1
11/1	2200	H	12	0	1	0	...	..	.068	35	180	51	90	1944	.....	5 p. m. 8 a. m.	1 1
12/1	2200	H	14	0	0	0	....	.....	. .	43	190	51	96	2086	.....	5 p. m. 8 a. m.	1 1
13/1	1550	II	12	0	0	0	....	.....	....	43	190	51	96	2086	118½	5 p. m. 8 a. m.	1 1
14/1	2300	H	12	0	1	0	....	. .		43	190	51	96	2086	.....	5 p. m. 8 a. m.	1 1
15/1		.	..	...	..	.	....	....	.115	43	190	51	96	2086	. ...	5 p. m. 8 a. m.	1 1
16/1																Discharged	

increase the diet gradually to a level 520 calories above the original calculated basal diet without glycosuria. In this patient, as in all our diabetics now, we allowed a hypoglycemic reaction to take place in order to have the patient recognize the symptoms, which are quite definite for the individual, and to experience the cure of these symptoms by administration of carbohydrate.

N. T., male, age 49 years; admitted, November 26, 1922.

Glycosuria discovered eleven years ago. He was always able to render himself sugar free by reduction in diet but as a rule did not take the trouble to do so. During the period of his disease his weight fell from 196 lb. to 168 lb. In October, 1922, he scraped the top of a corn off the third left toe. This area subsequently became infected and gangrene set in. On November 15 his toe was removed under gas and oxygen. It was then noted that there was no arterial pulsation in the operation area. Following the operation the wound broke down and the infection spread. On November 26 he was admitted with a cellulitis of the foot and ankle and with a glycosuria of 3½ per cent. and a blood sugar of .411 per cent. Up to this time some degree of dietetic control had been exercised. No quantitative estimations of the sugar excretion had been made, but it was known that the daily sugar excretion was increasing.

The laboratory findings, the dietetic treatment, and insulin administration are given in the accompanying table (Table VII). On November 26, at time of admission, the left foot and lower part of the leg was edematous; the skin was red and shiny. On pressure over the arch of the foot thick pus exuded from the wound. Patient was drowsy as a result of the ketosis; his pulse was weak. On November 27 he had a chill. No chills had taken place up to this time, but a chill occurred daily for the next few days. On November 28 patient was irrational and very weak. On November 29 blood culture was sterile. His temperature varied from 99° to 102° or 103° F. every day; pulse rate from 100 to 140. On December 6 a drainage tube was inserted into the subcutaneous tissue about the ankle. The septic temperature and rapid pulse continued up to December 14, but some improvement had occurred in the patient's general physical condition. On December 14 the leg was amputated through the middle of the thigh. Following the operation the temperature fell somewhat, but an irregular fever up to 101° F. persisted. The amputation flaps became infected; sloughs appeared which gradually separated. At the present date, January 29, the patient's general appearance has improved very much. He feels much better and is enjoying his food. The wound looks healthier and shows good prospects of healing.

This case is remarkable on account of the large amounts of insulin that could be given without fall in the fasting blood sugar levels or cessation of glycosuria. For instance, on December 2, total urinary nitrogen was 14.3 gm., indicative of combustion of 99.8 gm. of protein. This, with 140 gm. of fat and 40 gm. of carbohydrate of the diet, would yield 112 gm. of total glucose. On this day 80 units of insulin was given, which, according to our clinical estimation, should have a glucose equivalent of 160

gm. In spite of this large administration a slight degree of glycosuria persisted, the ferric chloride reaction was positive and the fasting blood sugar on the following morning was practically unchanged—.346 per cent. In other words, assuming that on this day he was an absolute diabetic, insulin would be required for 112 gm. only, of glucose; whereas sufficient insulin to insure the combustion of 160 gm. of glucose did not materially lower the blood sugar at the end of the 24 hr. period, nor prevent the occurrence of glycosuria. Allowing for a production of a small amount of insulin by the patient's own insular tissue, the discrepancy between the total glucose utilized and the carbohydrate equivalent of the available insulin would be still greater.

The prognosis of diabetes in children and young adults has been notoriously very bad. There is no doubt that much of the severity of the disease is due to neglect of the early warning symptoms and failure to carry out a proper dietetic regime. Nevertheless, the usual tendency, even in well controlled cases, is for progressive deterioration in tolerance to take place. A considerable percentage of our cases have been children and a large proportion young adults, though successful results are obtained in the aged diabetic as well. The youngest patient was a child of three years; the oldest a woman of seventy. Three coma cases were in children under ten years. Of these, two are now living. The three following case reports indicate the clinical value of insulin in children.

G. S., age 11, height 4 feet 9 inches, weight 66½ lb.; calculated basal caloric requirement 1306 calories; admitted September 23, 1922; discharged November 7, 1922. Complaint—polyuria and pruritus vulvae.

Fifteen months ago patient was perfectly well, then commenced vomiting, with frequent headaches; shortly, great thirst accompanied by polyuria developed. Urinalysis, October 26, 1921, showed the presence of sugar. Patient has been well supervised. For the first two months she was on a diet high in fat, on which she gained weight from 69½ lb. to 77¼ lb., but tolerance broke. Higher protein diet was tried with only temporary success and patient was taken to hospital and glucose tolerance determined and a diet prescribed. During the year there has been a progressive periodic loss of tolerance, and on admission patient was on a diet of protein 48 gm., fat 134 gm., carbohydrate 10 gm., with persistent glycosuria.

Past illnesses: Whooping-cough, age 2 years; mumps at 6 years; influenza and bronchitis at 7 years; tonsillectomy 2 years ago.

Family history: Negative for diabetes.

Examination: General—fairly well nourished child of 11 years; skin

TABLE VII—Patient N. T.
Age 49 Years. Height 5 Feet, 6 Inches. Weight 160 Pounds.

Date 1922	Urine								Blood Sugar %	Food Intake				Wt. Lb.	Insulin	
	Vol. cc.	R	Sp. G.	Sug. Gm.	Ketones			Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	cc.
					SNP	Fe Cl3	Mg.									
26/11																
5– 7 p.m.	200	H	1022	7.12	2	2	...	...	5 p.m.	...	...	..	....	...	.....	.
7– 9 p.m.	120	H	1020	2.47	2	2	...	3.9	.416	Fluid	Diet	..	....	...	5 p.m.	2
9–11 p.m.	50	H	.....	.44	2	2	...	...	9 p.m.	..	...	..	....	...	.....	.
11– 1 p.m.	100	..	.....	1.06	2	2	...	...	.392	..	...	..	....	...	.....	.
1– 3 a.m.	150	H	.....	2.64	2	2	...	...	1 a.m.	..	...	..	....	...	.....	.
3– 5 a.m.	300	H	.....	.....	.	.	...	...	.335	..	...	..	....	...	.....	.
									5 a.m.							
5– 7 a.m.	250	H	.....	.....	.	.	...	...	.350							
27/11									9 a.m.							
7– 9 a.m.	600	H	1020	17.46	2	2	...	...	.288	..	...	..	....	...	8 a.m.	2
									3.30 p.m.							
9–11 a.m.	38	H	1022	.67	2	2	...	13.8	.227	50	140	40	1620	...	5 p.m.	2
11– 1 p.m.	38	H	1022	1.08	2	2	...	...	.....	..	...	..	....	...	.....	.
1– 6 p.m.	300	H	1020	4.98	1	2	...	...	.....	..	...	..	....	...	.....	.
6– 6 a.m.	650	H	1020	1.26	2	2	...	...	.....	..	...	..	....	...	.....	.
															8 a.m.	2
28/11	2300	H	1018	62.1	2	2	...	9.2	.....	50	140	40	1620	...	5 p.m.	2
															8 a.m.	2
															12 n.	2
29/11	2300	H	1015	.46	2	1	...	9.6	.....	50	140	40	1620	...	5 p.m.	2
															8 a.m.	2
															12 n.	2
30/11	1100	H	1015	13.4	2	1	...	...	.290	50	140	40	1620	...	5 p.m.	2
															8 a.m.	2
															12 n.	2
1/12	3100	OH	1011	18.4	1	1	...	...	.....	50	140	40	1620	...	5 p.m.	2
															8 a.m.	2
															12 n.	3
2/12	3250	OH	1010	0.97	2	1	...	14.3	.350	50	140	40	1620	...	5 p.m.	3
															8 a.m.	3
															12 n.	3
3/12	3000	H	1010	6.3	1	0	...	...	.346	50	140	40	1620	...	5 p.m.	3
															8 a.m.	3
															12 n.	3
4/12	3100	H	1008	0	1	0	...	13.3	.....	50	140	40	1620	...	5 p.m.	3
															8 a.m.	3
															12 n.	3
5/12	2150	H	1011	.86	1	0	720	9.7	.277	50	140	40	1620	...	5 p.m.	3
															8 a.m.	2
															12 n.	2
6/12	3950	H	1008	9.4	1	0	1568	13	.....	50	140	40	1620	...	5 p.m.	2

															8 a.m.	2
															12 n.	2
7/12	4450	H	1010	22.47	1	0	. .	. .	.365	50	140	40	1620	...	5 p.m.	2
8/12	3465	H	1011	16 5	1	0	. .	. .	. . .	50	140	40	1620	...	5 p.m.	2
															8 a.m.	2
															12 n.	3
9/12	2850	OH	1015	32 7	1?	0	. .	. .	.403	75	100	150	1800	...	5 p.m.	3
															8 a.m.	3
															12 n.	3
10/12	3100	H	1012	49.9	1	0	...	...	. . .	75	100	150	1800	...	5 p.m.	3
															8 a.m.	3
															12 n.	3
11/12	3050	H	1012	32.4	1	0	. .	11 5	.294	75	100	150	1800	. .	5 p.m.	3
															8 a.m.	3
															12 n.	3
12/12	2550	H	1017	0	1?	0	...	11.4	. . .	75	100	150	1800	. .	5 p.m.	4
															8 a.m.	4
															12 n.	4
13/12	2300	H	1018	36.1	1	0	.	11.5	. .	75	100	150	1800	. .	5 p.m.	4
															8 a.m.	2
															12 n.	2
14/12	1350	H	1022	40 5	2	0	911	7 1		Ope	ration		....	...	5 p.m.	2
															8 a.m.	3
															12 n.	3
15/12	1350	H	1022	39 4	1?	0	.	. .	.	75	100	150	1800	...	5 p.m.	3
															8 a.m.	4
															12 n.	4
16/12	1200	H	1016	16 8	1?	0	.	.		75	100	150	1800	...	5 p.m.	4
															8 a.m.	4
															12 n.	4
17/12	2150	OH	1013	2.025	2	0	512	. .	. .	75	125	75	1725	.	5 p.m.	4
															8 a.m.	4
															12 n.	4
18/12	1900	H	1010	1 0	1?	0	.	. .	.367	75	125	75	1725	. .	5 p.m.	4
															8 a.m.	4
															12 n.	4
19/12	1800	H	1010	trace	1?	0	.	.	.	64	88	49	....	...	5 p.m.	4
															8 a.m.	4
															12 n.	4
20/12	1150	H	1010	0	0	0	. .	. .	241	5	17	23	265	...	5 p.m.	4
															8 a.m.	4
															12 n.	4
21/12	1700	H	1010	0	1	0	. .	...	.231	75	125	40	1585	. .	5 p.m.	4
															8 a.m.	4
															12 n.	4
22/12	2350	..	1008	0	0	0	...	...	....	75	125	40	1585	...	. . . . .	.
															8 a.m.	2
															12 n.	2
23/12	1700	H	1010	0	0	0	...	...	....	75	125	40	1585	...	5 p.m.	2

TABLE VII.—*Continued*

Date 1922	Urine								Blood Sugar %	Food Intake				Wt. Lb.	Insulin	
	Vol. cc.	R	Sp. G.	Sug. Gm.	Ketones			Tot. Nit.		Prot.	Fat	CHO	Tot. Cal.		Time	cc.
					SNP	FeCl3	Mgs.									
24/12	1700	H	1010	0	0	0	...	...	.229	62	125	40	1553	...	8 a.m. 12 n. 5 p.m. 8 a.m.	2 2 2 2
25/12	2600	H	1007	0	1	0	...	...	....	62	125	40	1553	...	12 n. 5 p.m. 8 a.m.	2 2 2
26/12	2100	H	1010	0	0	0	...	...	.235	63	115	40	1447	...	12 n. 5 p.m. 8 a.m.	2 2 2
27/12	2200	H	1007	0	1?	0	...	...	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
28/12	2250	H	1010	0	0	0	...	10.8	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
29/12	2200	H	1010	0	1	0	...	...	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
30/12	3050	H	1010	0	0	0	...	...	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
31/12	3100	H	1010	0	0	0	...	...	.223	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
1923 1/1	2400	H	1010	0	0	0	...	...	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
2/1	2200	H	1011	0	0	0	...	...	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
3/1	2750	H	1010	0	0	0	...	...	....	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
4/1	2200	H	1012	0	0	0	...	10.7	.125	75	125	40	1585	...	12 n. 5 p.m. 8 a.m.	2 2 2
5/1	1950	H	1010	0	0	0	...	...	....	75	125	60	1665	...	12 n. 5 p.m.	2 1

																8 a.m.	1
																12 n.	1
6/1	2200	H	1011	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
																12 n.	1
7/1	2250	H	1010	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
																12 n.	1
8/1	2000	H	1015	0	0	0	...	...	.165	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
																12 n.	1
9/1	2550	H	1013	0	0	0	...	11.4	....	75	125	45	1605	...		5 p.m.	1
10/1	1850	H	1012	0	1?	0	...	8.9	.185	75	125	45	1605	...		8 a.m.	1
																5 p.m.	1
11/1	2250	H	1011	0	1?	0	...	...	....	75	125	45	1605	...		8 a.m.	1
12/1	2300	H	1012	0	0	0	...	...	....	75	125	45	1605	...		5 p.m.	1
																8 a.m.	1
13/1	2300	H	1012	0	0	0	...	...	.133	75	125	45	1605	...		5 p.m.	1
																8 a.m.	1
14/1	2250	H	1012	0	1?	0	...	...	....	75	125	45	1605	...		5 p.m.	1
																8 a.m.	1
15/1	3000	H	1013	0	1?	0	...	...	.219	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
16/1	2300	H	1012	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
17/1	3000	H	1012	0	1?	0	...	...	.143	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
18/1	2300	H	1010	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
19/1	2200	H	1013	0	0	0	...	...	.171	75	125	50	1625	...		5 p.m.	1
																8 a.m.	1
20/1	2250	H	1012	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
21/1	2250	H	1012	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
22/1	2100	H	1012	0	0	0	...	...	.151	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
23/1	1100	H	1012	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
24/1	2250	H	1015	0	0	0	...	...	.172	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
25/1	2250	H	1013	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
26/1	2200	..	....	0	0	0	...	...	....	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
27/1	1800	H	....	0	0	0	...	...	.220	75	125	40	1585	...		5 p.m.	1
																8 a.m.	1
28/1	1400	H	1013	0	0	0	...	...	...	75	125	40	1585	...		5 p.m.	1

dry and pale, but in fair condition. Respiratory system—well developed chest, moving freely, symmetrically and synchronously; breath sounds normal; percussion note normal. Circulation—nothing abnormal found. Digestive system—teeth, gums, tongue, throat in good condition; nothing abnormal in abdomen. Nervous system—intelligent, but tired and languid; eyes react to light and accommodation; biceps jerks normal; knee jerks could not be elicited.

On admission to hospital the patient was given a diet of protein 25 gm., fat 118 gm., carbohydrate 36 gm., calories 1307, and excreted 7.4 gm. of sugar. She promptly became sugar free on two days when non-nutrients only were allowed, but on the following day the glucose excreted was again 7.4 gm. Blood sugar 0.151 per cent., acetone 1.2 gm. per day. Following this time the patient was not complaining of any definite illness but did not feel as well as usual and was re-examined carefully without evidence of a pathological condition being found. The temperature repeatedly rose to 99° F., or even a little higher. The glycosuria steadily increased to 36 gm. per day; the acetone bodies to 2.7 gm., and approximately 2 gm. more nitrogen were excreted than on the same diet previously. We believe that here we have observed one of a series of periodic losses of tolerance due to infection, similar to those which she had experienced before. The diet was reduced to protein 25 gm., fat 126 gm., carbohydrate 23 gm., following the Wilder formula. This was 13 gm. less carbohydrate than she had previously received, and the excretion was 14 gm. less on this date and still less the following day, but at the end of five days had again risen to 34 gm. with a rise in blood sugar to 0.234 per cent., and a further increase of 1 gm. in the urinary nitrogen. The acetone body excretion reduced at first but rose again with the intolerance for carbohydrates. Insulin was used with the result of getting the patient sugar free on the second day, but the blood sugar rose and glycosuria again appeared and was controlled by further amounts of insulin. With this addition she became sugar free; the acetone bodies disappeared from the urine and the blood sugar fell to normal, and later, to guard against hypoglycemic reaction, the insulin dosage had to be reduced. It is interesting to note the increase in weight of this patient on a basal diet. Cf. Table VIII.

A. K., age 8 years, height 3 feet, 4½ inches, weight 24½ lb.; calculated caloric requirement 886 calories; admitted to hospital November 11, and discharged December 11, 1922; re-admitted January 3, 1923.

Diagnosed diabetes mellitus at 2½ years of age. Symptoms—frequency, bed-wetting, thirst, and glycosuria. On discovery of the condition was placed on a diet, but was not made to adhere to it in a systematic manner. On becoming worse and decreasing in weight, he was placed under treatment for a time, but the strictness of treatment was repeatedly relaxed at intervals, and he gradually lost tolerance. During the past summer he was aglycosuric for a long period on 850 calories, but later, following uncontrolled feeding, was unable to be made sugar free on 624 calories, on which diet he was admitted to the Toronto General Hospital.

Past illnesses: Measles at 3 years, followed by bronchitis and influenza.

Family history: Negative for diabetes.

Examination: General—Remarkably intelligent, eight year old child. In general physique markedly emaciated, and appearing like a little old man. Teeth good, tongue clean and moist. Throat normal. Tonsils small and apparently normal. Fundi normal. Ear drum membranes normal. Palpable cervical glands. Thyroid not enlarged. Circulation—No cyanosis, edema, dyspnea, or abnormal pulsations. Slight anemia. Heart normal in size; sounds good quality; functional systolic murmur sometimes present; pulse regular, good quality; rate 96 per min. All arteries palpated more easily than normal, due in part to thickening of vessels, and partly to the emaciation. Respiratory system—Chest emaciated. rather flat; movements free, equal, synchronous and symmetrical. V.F. and V.R. normal. Percussion note slightly hyper-resonant. Puerile breathing. No adventitious sounds. Nervous system—Intelligence at least equal to 12 year old normal; education—nil. Eyes react to light and accommodation for distance is present. No sensory changes found. Co-ordination good. Tendon reflexes absent. Abdomen—distended with gas; no rigidity or tenderness; liver palpable; otherwise normal. G.U. system—Genitals atrophic. Has nycturia and polyuria. No difficulty, no burning. Skeletal system—No evidence of rickets or other bone disease. X-ray shows delayed development of centres of ossification.

The child entered hospital on a diet of: protein 60 gm., fat 36 gm., carbohydrate 20 gm.; calories 624. Weight 24½ lb. Blood sugar .220 per cent.; sugar in urine 36 gm.; acetone present in small amount. He was placed on a diet of: protein 17 gm., fat 80 gm., carbohydrate 24.5 gm.; calories 886, for 10 days, during the last four of which the daily excretion of sugar was 20 gm. 7.5 units of insulin at 5 p.m. on November 21 reduced the excretion of sugar to 13 gm., the fasting blood sugar to .093 per cent., and cleared up the acetone bodies from the urine, and the next day on two doses of 7.5 units being given (at 8 a. m. and 5 p. m.) he became sugar free and remained so except on one occasion following the excessive administration of sugar during a slight hypoglycemic reaction, and a later occasion when surreptitious ingestion of food seems to be the only possible explanation, as he was sugar free for some days before and thereafter until discharge on the same dose of insulin; and his blood sugar on this date was extraordinarily high. Acetone bodies disappeared from the urine on the first day, and have never occurred in significant amounts since, though the Rothera reaction has been faintly positive on a few occasions. The blood sugar has been 0.13 per cent., or below, most of the time, except following the treatment of hypoglycemia and addition of 200 calories to his diet in the form of 5 gm. carbohydrates and 20 gm. of fat, when it rose to 1.83 per cent. to fall again to .138 per cent on the morning of discharge, December 11, 1922. The weight increased from 24½ lb. to 28 lb. He was re-admitted on January 3, 1923. He has been sugar free for 16 out of 18 days. He acquired a severe streptococcal tonsillitis with a generalized erythema and pruritus, and enlargement of the lymphatic glands. During this period of raised temperature the child remained in bed, and his glucose tolerance appeared to be unaffected. He remained on the same dose of insulin and same

TABLE VIII.

Patient G. S.

Age 11 years. Height 4 feet 9¼ inches. Weight 66½ pounds. Surf. Area 1.12 sq. m.

Date	Urine								Blood Sugar %	Food Intake					Wt. lb.	Insulin	
	Vol. cc.	R	Sp. G.	Sug. Gm.	Ketones SNP	Ketones FeCl3	Ketones Mg.	Tot. Nit.		Prot.	Fat	CHO	Total Glucose	Tot. Cal.		Time.	cc.
1922																	
23/9	800	H	14	7.4	1	1	526	3 41	...	25	118	36	62	1304	66½	....	...
24/9	2350	H	06	0	1	1	1136	6.41	...	Non Nutrients		..	..	....	....	....	...
25/9	2200	H		0	1	0	343	6.30	...	Non Nutrients		..	..	....	....	....	...
26/9	2350	H	07	7.4	1	0	....	5.90	.151	25	118	36	62	1304	....	....	...
27/9	3200	H	06	12.1	1	0	1181	7.43	...	25	118	36	62	1304	....	....	...
28/9	2450	H	07	12.1	1	0	....	8.62	...	25	118	36	62	1304	....	....	...
29/9	2800	H	10	26 7	1	0	500	8.61	...	25	118	36	62	1304	....	....	...
30/9	300	H	06	18 0	1	0	766	11.82	...	25	118	36	62	1304	....	....	...
1/10	4800	H	10	36.2	1	0	2688	8.72	...	25	118	36	62	1304	....	....	...
2/10	2650	H	10	22.1	1	0	1110	.....	...	25	126	23	50	1326	67¼	....	...
3/10	2300	H	12	11.2	1	0	1375	8 61	...	25	126	23	50	1326	....	....	...
4/10	3000	H	10	28.6	1	0	1548	7.97	...	25	126	23	50	1326	....	....	...
5/10	2550	H	10	24.8	1	0	827	8.82	...	25	126	23	50	1326	....	....	...
6/10	3450	H	11	34.0	1	0	2220	9.8	.234	25	126	23	50	1326	....	....	...
7/10	1330	H	05	4.96	1	0	834	7 7	.235	25	126	23	50	1326	....	12 N	2
8/10	2600	H	06	0	1	0	52	7.8	.252	25	126	23	50	1326	....	12 M	2
9/10	3650	H	07	1	1	0	....	7.2	.338	25	126	23	50	1326	....	12 N	2
10/10	2600	H	09	5.3	1	.	213	6.9	.239	25	126	23	50	1326	68¾	12 N	2
																12 N	1
11/10	3650	H	07	10.4	1	0	0	6.93	.239	25	126	23	50	1326	....	5 p. m.	1
																12 N	1
12/10	3650	H	06	+	1	0	0	.....	.225	25	126	23	50	1326	....	5 p. m.	1
7-12	180	H	07	0	0	0	0										
12-7	1100	H	06	0	0	0	0									12 N	1½
7-7	1600	H	10	0	0	0	0	7.42	.196	25	126	23	50	1326	68¾	5 p. m.	1½
7-12	1100	H	06	0	1	0	18										
12-7	900	H	07	0	1	0	20									12 N	1½
7-7	1400	H	08	0	0	0	0	9.28	.218	25	126	23	50	1326	....	5 p. m.	1½
7-12	700	H	06	0	0	0	0										
12-7	500	H	06	0	0	0	0									12 N	1½
7-7	1600	H	06	0	1	0	0	8.87	.237	25	126	23	50	1326	....	5 p. m.	1½
																12 N	1½
16/10	3000	H	08	0	0	0	0	6.72	.210	25	126	23	50	1326	71½	5 p. m.	1½
																12 N	1½
17/10	3000	H	05	3.6	1†	0	0	5.88	...	25	126	23	50	1326	....	5 p. m.	1½
																12 N	1½
18/10	3250	H	08	0	1	0	0	8.54	.181	25	126	23	50	1326	....	5 p. m.	1½

19/10	3250	H	..	1 6	1	0	1030	7.00	.114	25	126	23	50	1326	....	12 N	1½
7-12	1000	H	06	0	1	0	0									5 p. m.	1½
12-7	1150	H	06	0	1	0	0									12 N	1½
7-7	1800	H	06	0	0	0	0	7.74	.136	25	126	23	50	1326	....	5 p. m.	1½
7-12	850	OH	09	0	0	0	....										
12-7	1300	H	07	0	0	0	....									12 N	1½
7-7	1350	H	08	0	0	0	....	7.35	...	25	126	23	50	1326	....	5 p. m.	1½
																12 N	1½
22/10	1100	OH	09	0	1	0	....	6.1	...	25	126	23	50	1326	....	5 p. m.	1½
7-12																	
12-7	500	H	10	0	0	0	....									12 N	1½
7-7	1450	H	10	0	0	0	....	6.1	.116	25	126	23	50	1326	71¼	5 p. m.	1½
																12 N	1½
24/10	3450	H	05	0	0	0	....	8.6	...	25	126	23	50	1326	71¼	5 p. m.	1½
																12 N	1½
25/10	2850	H	10	0	0	0	....	6.8	.121	25	126	23	50	1326	....	5 p. m.	1½
																12 N	1
26/10	3100	H	07	0	1	0	....	8.2	...	25	126	23	50	1326	72¼	5 p. m.	1
																12 N	1
27/10	3300	H	08	0	1	0	....	7.3	.108	25	126	23	50	1326	71¼	5 p. m.	1
																12 N	1
28/10	2500	H	08	0	1	0	....	8.2	...	..	....	..	..	....	71¼	5 p. m.	1
																12 N	1
29/10	2750	H	08	0	1	0	....	12.1	.12	25	126	23	50	1326	....	5 p. m.	1
																12 N	1
30/10	2700	H	08	1.22	1	0	....	.....	...	25	126	23	50	1326	71¼	5 p. m.	1
																12 N	1
31/10	3350	H	06	0	1	0	....	8.2	.09	25	126	23	50	1326	73¼	5 p. m.	1¼
																12 N	1¼
1/11	2600	H	09	0	1	0	....	8.5	.11	25	126	23	50	1326	70¾	5 p. m.	1¼
																12 N	1¼
2/11	3150	H	10	1.35	1	0	....	8.1	.1	25	126	23	50	1326	70	5 p. m.	1¼
																12 N	1¼
3/11	3550	H	07	0	0	0	....	7.9	.116	25	126	23	50	1326	70½	5 p. m.	1¼
																12 N	1¼
4/11	3100	H	10	0	0	0	....	10.5	...	25	126	23	50	1326	....	5 p. m.	1¼
																12 N	1¼
5/11	3150	H	06	0	1	0	....	7.5	.105	25	126	23	50	1326	....	5 p. m.	1¼
																12 N	1¼
6/11	3250	OH	07	0	1	0	....	6.8	...	25	126	23	50	1326	71	5 p. m.	1¼
																12 N	1¼
7/11	....	..	..	...	.	.	....	.....	...	25	126	23	50	1326	70½	5 p. m.	1¼
															Discharged 5 p. m.		

diet as on admission. The interesting point during this period seemed to be a pronounced increased tendency to hypoglycemic reactions, of which he had several during the fever.

E. H., female, age 15 years, height 5 feet, weight 45 lb.; admitted August 16, 1922; discharged December 1, 1922.

Present illness: In the fall of 1918 polydipsia and polyuria appeared following a period of frequent colds. She complained of increasing weakness. During the winter she suffered from pains in the legs and back and from insomnia. In March, 1919, these symptoms became more severe. The appetite became excessive and there was some pruritus. The weight by this time had fallen from 75 lb. to 62 lb. Glycosuria was discovered and she was placed under the care of Dr. F. M. Allen, to whom we are very much indebted for a complete record of the case from April, 1919, up to the time of admission, August, 1922. During this period the diet was controlled so as to maintain the urine free of sugar. The accompanying chart (Chart I) shows (a) the daily calories of the food, an average being made for each month; (b) the average for each month of the total daily available carbohydrate of the food; and (c) the weight of the patient at monthly intervals. Despite the careful dietetic regime the patient's condition became progressively worse. On admission her weight was 45 lb.

Past illnesses: Patient was never strong. Measles twice, as a child. Tonsillectomy at age of 5 years and again at age of 12 years. Appendectomy, March, 1917.

Family history: One sister died of tuberculosis. No family history of diabetes.

Examination: Patient emaciated; skin dry; slight edema of ankles. Hair brittle and thin. Abdomen prominent. Marked weakness. Nothing of note in the respiratory, cardiovascular, digestive or nervous system.

Treatment: At the time of admission she was receiving a diet of protein 50 gm., fat 71 gm., carbohydrate 20 gm. Insulin treatment was started immediately and the diet was increased daily so that, at the end of two weeks, she was receiving protein 63 gm., fat 208 gm., carbohydrate 97 gm., equaling 2512 calories. This diet was continued approximately at this level up to January 1, 1923. Insulin was given 15 to 30 minutes before the morning and evening meals. A sufficient amount was given to maintain the urine free of sugar. Each specimen of urine was examined and the dose was increased slightly if traces of sugar appeared. When hypoglycemia occurred orange juice or glucose candy was given. Between August 16 and January 1 the urine was sugar free except on ten occasions when traces of sugar appeared, and on two other occasions when less than 2 gm. was excreted. Acetone was absent from the urine.

On this treatment the patient gained rapidly in strength and in weight, and was soon able to take vigorous exercise. The diet included such food stuffs as cereals, bread, potato, rice, corn, tapioca, corn starch, and even honey.

Insulin was discontinued for four days to determine any change in her ability to utilize carbohydrate as a result of three months' treatment.

CASE E.H.
AVERAGE DAILY CALORIC INTAKE.
AVERAGE DAILY AVAILABLE CARBOHYDRATE IN GRAMS.
WEIGHT IN POUNDS.
INSULIN INJECTIONS COMMENCED AUGUST 14TH 1922.
1919
1920
1921
1922

From July 14 to August 1, 1922, the patient had remained sugar free on a diet of protein 50 gm., fat 71 gm., carbohydrate 20 gm., except for one day a week when half this amount was given. On August 1, 2 gm. of fat were added daily so that on August 5 she received protein 50 gm., fat 81 gm., carbohydrate 20 gm. On August 6 sugar appeared in the urine and the diet was reduced. On November 16 insulin was discontinued and the diet of protein 50 gm., fat 71 gm., carbohydrate 20 gm., again given. On the fourth day sugar appeared in the urine and insulin was continued again. Apparently there has been no increase in her power to utilize carbohydrates during these three months of treatment.

Subsequent history: On December 1 patient returned home. She now arranges her own diets, makes her own tests, administers insulin to herself, and keeps her own records. Three mornings a week she rides horseback for two hours. The other three mornings she swims. She has returned to school. She has grown ¾ of an inch. Weight is now 93 lb. She appears to be in good health. The case is remarkable for the increase in weight—45 lb. to 93 lb. in five months.

It may be of interest to tabulate the results of the urine analyses of all patients in our clinic receiving insulin for a period, and compare the results with the urine analyses of the same patients on a basal diet and receiving no insulin. The period January 5 to 11, 1923, was arbitrarily chosen, and the results appear in Table IX.

The patients receiving insulin during the week numbered 15. Twelve of these patients we had been unable to make sugar free on a basal caloric diet. One entered as a post-operative emergency case, and two were given insulin because of persistent hyperglycemia on a basal diet, in order to raise the caloric intake and because, as Fletcher has shown, low blood sugar levels improve an arthritis in some cases and, in fact, did in this case. These patients, during the week of January 5 to January 11, were on varying diets, ranging from their basal caloric requirement up to 1400 calories above this, and the total number of positive sugar reactions was eleven, which may be analyzed as follows:

Case Hk. Cause of glycosuria unknown.

Case L. Stealing food.

Case P. Showed glycosuria on 6 days. Owing to danger of inanition coma, no attempt was made to keep patient sugar free. He was given insulin and 100 gm. carbohydrate, and as much other food as he would eat.

Case W. Glycosuria resulted from overdose of carbohydrate used to control hypoglycemia.

TABLE IX

Initials	Test	Date: January							Remarks
		5	6	7	8	9	10	11	
B	Glucose	0	0	0	0	0	0	0	
	Rothera	tr.	0	tr.	tr.	tr.	0	tr.	
	$FeCl_3$	0	0	0	0	0	0	0	
D	Glucose	0	0	0	0	..	..	..	Discharged Jan. 9.
	Rothera	0	0	0	0	..	..	..	
	$FeCl_3$	0	0	0	0	..	..	..	
E	Glucose	0	0	0	0	0	0	0	
	Rothera	tr.	0	tr.	tr.	tr.	0	tr.	
	$FeCl_3$	0	0	0	0	0	0	0	
Hd	Glucose	0	0	0	0	0	0	0	
	Rothera	tr.	0	0	0	+	0	0	
	$FeCl_3$	0	0	0	0	?	0	0	
Hk	Glucose	0	0	0	5.0	0	0	0	Glucose, gm. per 24 hr.
	Rothera	tr.	0	tr.	+	tr.	tr.	+	
	$FeCl_3$	0	0	0	+	0	0	?	
Kr	Glucose	0	0	0	0	0	0	0	
	Rothera	tr.	0	tr.	?	tr.	tr.	?	
	$FeCl_3$	0	0	0	0	0	0	0	
Kz	Glucose	0	0	0	0	0	0	0	
	Rothera	tr.	0	tr.	tr.	tr.	0	+	
	$FeCl_3$	0	0	0	0	0	0	?	
L	Glucose	3.8	46	9.8	0	0	0	0	
	Rothera	0	0	0	tr.	0	0	+	
	$FeCl_3$	0	0	0	0	0	0	0	
M	Glucose	0	0	0	0	0	0	0	Sugar free on basal diet.
	Rothera	tr.	0	tr.	+	tr.	tr.	0	
	$FeCl_3$	0	0	0	0	0	0	0	
P	Glucose	1.0	2.7	6.9	4.4	0	3.9	2.2	
	Rothera	0	0	0	0	0	0	0	
	$FeCl_3$	0	0	0	0	0	0	0	
S	Glucose	0	0	0	0	0	0	0	
	Rothera	0	0	0	0	0	0	0	
	$FeCl_3$	0	0	0	0	0	0	0	
Tu	Glucose	0	0	0	0	0	0	0	
	Rothera	0	0	0	tr.	0	0	0	
	$FeCl_3$	0	0	0	0	0	0	0	
Tr	Glucose	0	0	0	0	0	0	0	
	Rothera	0	0	0	0	0	0	0	
	$FeCl_3$	0	0	0	0	0	0	0	
Ts	Glucose	0	0	0	0	?	0	?	After recovery from coma.
	Rothera	..	0	tr.	tr.	+	+	+	
	$FeCl_3$	0	0	0	0	?	0	?	
W	Glucose	0	1.7	0	0	0	0	0	
	Rothera	0	0	0	0	0	0	0	
	$FeCl_3$	0	0	0	0	0	0	0	

In the tests carried out for ketones we define as a "trace" those Rothera reactions developing a permanganate color after several minutes. Repeated quantitative examination of such specimens shows that never more than 250 mg. of ketones per 24 hours are present, and usually very much less. 31 Rothera tests are listed as traces, and it is probable that all these could have been prevented at will by readjustment of the proportions of fat and carbohydrate in the evening meal, but as the amounts were clinically insignificant this has not been done except in a few cases. 10 positive Rothera reactions also occurred, four in a patient who was in coma on Christmas day. One positive and five doubtful ferric chloride reactions occurred. These accompanied positive Rothera reactions, and in no case indicated an uncompensated acidosis. Results equally as good could have been shown by extending the table forward or backward, but this would have introduced new cases just commencing insulin treatment, and others would have been discharged before the end of the period.

These patients entered hospital at various times and so, for comparison, the last seven days of their period of observation on basal diet is taken. The results are given in Table X.

Discussion

The severe diabetic presents a problem to clinical medicine which is unique in that there is no other condition which gives rise to so great a derangement of the metabolism of all the foodstuffs. In the lesser degrees of the disease, adequate control is obtained by modern dietetic methods of treatment. When the production of insulin by the pancreas falls below a certain minimum, however, no dietetic method of treatment will stay the progress of the disease. The artificial administration of insulin in addition to dietetic treatment furnishes the only hope for these patients and, as shown in the following paper,[4] is effective even during coma. The present paper illustrates a general method of examination and the treatment of a number of severe cases of diabetes mellitus by insulin, and the results obtained.

Consideration of the energy requirements of the body led us to adopt as a standard level, to which all diabetics should attain, the normal basal caloric requirement for their age, height, weight and sex. A period of observation on a diet constructed as outlined above showed in certain cases an inability to properly metabolize sufficient foodstuffs to attain this end. These patients were treated with insulin, and without exception have been

TABLE X

Initials	Test								
B	Glucose	21.3	31.2	14.7[z]	24.9	25.2	20.1	16.5	[z]Non nutrients.
	Rothera	+	tr.	+	+	+	+	+	Glucose in gm. per 24
	$FeCl_3$	+	+	+	+	+	+	0	hours.
D	Glucose	64.5	45.4	46.7	32.2	40.5	35.6	47.5	
	Rothera	+	+	+	+	+	+	+	
	$FeCl_3$	+	+	+	+	+	+	+	
E	Glucose	52.5	58.5	66.5	63.7	47.4	52.9	37.1	
	Rothera	+	+	+	+	+	++	++	
	$FeCl_3$	+	+	+	+	+	+	+	
Hd	Glucose	+	+	42	45	6.7	5.9	4.8	+Not transferred to
	Rothera	x	+	+	+	tr.	+	0	clinic.
	$FeCl_3$	x	x	0	0	0	0	0	
Hk	Glucose	+	41	7.8	29.1	1.5	14.4	+	Child 5 yrs. Specimens
	Rothera	+	+	+	..	tr.	tr.	tr.	lost. Refused food at
	$FeCl_3$	0	0	0	0	tr.	0	0	times.
Kr	Glucose	Traces of acetone only.							Sugar free on basal diet.
	Rothera								Insulin used to lower
	$FeCl_3$								blood sugar.
Kz	Glucose	17.4	23.2	12	17.9	19.5	18.5	22	
	Rothera	tr.	tr.	+	+	+	+	+	
	$FeCl_3$	?	?	0	?	?	?	0	
L	Glucose	103	50	34.5	9.2	+	93	71	
	Rothera	+	+	+	+	tr.	+	+	
	$FeCl_3$	+	?	tr.	0	0	?	?	
M	Glucose	0	0	0	0	0	0	0	Sugar free on basal diet.
	Rothera	+	+	+	tr.	+	+	+	Given insulin for hyper-
	$FeCl_3$	0	tr.	0	0	tr.	tr.	tr.	glyeemia and arthritis.
P	Glucose	37	32	24	24	49	36	12.6	
	Rothera	+	++	++	++	++	++	++	
	$FeCl_3$	0	?	+	+	+	+	+	
S	Glucose	x	x	26	24	24	34	21.2	xNot yet on basal diet.
	Rothera	x	x	tr.	0	tr.	tr.	0	
	$FeCl_3$	x	x	0	0	0	0	0	
Tn	Glucose	44	62	19	24	32	29	24	
	Rothera	+	+	+	+	+	+	+	
	$FeCl_3$	?	?	?	?	?	?	?	
Tr	Glucose	Admitted to clinic with post operative cellulitis of leg and severe acidosis. Given insulin immediately.							
	Rothera								
	$FeCl_3$								
Ts	Glucose	x	x	34.4	26.7	lost	0[1]	33.1	Coma supervened follow-
	Rothera	x	x	++	+	lost	++	++	ing otitis media. [1]: fast-
	$FeCl_3$	x	x	+	+	lost	++	+	ing. x: not on diet.
W	Glucose	38	61	66	49	73	35	45	
	Rothera	+	+	+	+	+	+	+	
	$FeCl_3$	?	?	?	?	?	?	?	

benefited by the treatment. The daily subcutaneous administration of insulin does not result in great inconvenience and its use provides relief for most, if not all, of the symptoms immediately associated with the disease, except the desire for a normal diet. Glycosuria and ketonuria have been abolished. Blood sugar can be maintained at any desirable level, and most striking of all has been the improvement in the mental and physical attitude of the patient.

The diet of a diabetic may be raised to any desired amount and the patient remain aglycosuric, providing sufficient insulin is administered. However, one must not conclude that, in increasing the diet to satisfy the desires of the patient, the proper balance of protein, fat and carbohydrate can be neglected. Further, it is not advisable to increase the diet beyond such levels as will satisfy reasonable normal demands for energy. Increased nutrition calls for both increased insulin and increased food. This not only involves greater frequency of injections but, with greater caloric intake, there is a greater liability to either high blood sugars or else to hypoglycemic reactions. Some patients maintain their weight, even a degree of obesity, with diets slightly above their basal requirement. In others larger diets are required to maintain the body weight 20 per cent. below normal. In these patients we have attempted to raise the weight to this level but not further, and have supplied them with diets 30-50 per cent. above their normal basal requirements. Under insulin treatment there seems to be no need to maintain the more extreme forms of undernutrition which have been necessary in certain cases in the past. Such undernutrition results in limitation of both mental and physical efficiency. It increases the liability to and the severity of most infections, in addition to the hardship of rigid dietetic restriction.

A similar question is raised as to the necessity of maintaining normal blood sugars during treatment. Blood sugars well above normal provide some protection against the occurrence of hypoglycemia, and also allow greater economy in the use of insulin. But it hardly seems justifiable to abandon as a principle in treatment the maintenance of the blood sugar at a normal level. Hyperglycemia may be a factor in some of the degenerative processes—such as, arteriosclerosis, optic neuritis, and so on,—and besides this, blood sugars above the normal level must throw a greater load upon the islet tissue of the pancreas and encroach

upon the rest to this organ, which is made possible by insulin administration.

Rest for a weakened organ is a fundamental principle of therapeutics. A measure of rest can be furnished by dietetic control and it has been often shown, notably by Allen and Joslin, that this may result in increased power of carbohydrate utilization but, on the whole, the success of these dietetic restrictions in the severe case has been disappointing. It is known, however, that the power of carbohydrate utilization may undergo very considerable variation, and it seemed possible that the degree of rest made possible by the use of insulin might in certain cases bring about sufficient increased carbohydrate tolerance as to make it possible to dispense with its continual administration. Probably the milder cases offer the most hopeful field in this regard, for it is in these cases that the greatest gain in carbohydrate tolerance is brought about by dietetic control. But the necessity for economy in the use of insulin has confined us largely to the severe or emergent case; and when insulin has been administered to a mild case this has not been done until dietetic control has been carried out for several days.

In estimating the maximum power of carbohydrate utilization in a patient certain difficulties are met with. Healthy islet tissue probably shows wide variations in its production of insulin under different conditions, and it is also true that, to a less degree, this output may vary in the diabetic. Variations in sugar utilization occur in emotional disturbances, in infections, as a result of exercise, on the giving of carbohydrate before food, by increasing the diet, and so on. In the severe diabetic these factors do not exert so much influence but they are to be considered. Changes in the diet especially appear to be a source of error and it is questionable whether carbohydrate utilization during high diets can be compared with that observed on low diets. It would also appear that insulin production varies with the blood sugar level. Rising blood sugars act as a stimulus to pancreatic activity for a time. High blood sugars appear rapidly to fatigue the insular tissue.

Change in the amount of total glucose in the body, for which insulin is required for utilization, may influence the apparent amount of carbohydrate combustion. There is normally approximately 5 gm. of glucose in the circulating blood, and in the diabetic sometimes as much as four or five times this amount.

The amount present in the tissues and body fluids may be four and five times the normal amount, so that 100 gm. or more of glucose may be drawn on or stored during a period of observation. This would be accompanied, of course, by changes in the fasting blood sugar level.

Another factor, which possibly does not play so great a part, is the change in the condition of nutrition of the patient and, as a result, a change in the total metabolism. However, a knowledge of the carbohydrate administration in excess of the glucose excretion, and also of the urinary nitrogen, furnishes a fairly accurate estimate of the carbohydrate utilization even when the fat combustion is calculated on the basis of a normal caloric requirement.

In most cases to which insulin is given an estimate of the carbohydrate tolerance is first made during the preliminary period of observation while the patient is on a constant basal diet. When there has been suitable diet regulation before coming under observation the sugar excretion does not materially vary throughout the course of the observation period, and the daily carbohydrate utilization may be taken as the maximum carbohydrate tolerance that can be secured by dietetic measures. After a course of insulin administration an effort is made to estimate again the carbohydrate utilization power. It appears that a proportion of patients do regain a measure of increased power of carbohydrate utilization under insulin therapy. Increases in total glucose tolerance as much as 20-30 gm. have several times been observed. This increase in carbohydrate utilization power appears to persist as long as excessive demands are not made on the islet tissue of the pancreas by excessively high diet or high blood sugar levels. In other patients it may be stated that no increase in carbohydrate tolerance has been obtained.

The untreated diabetic is very prone to the development of complications and even when well treated enjoys no more, and probably somewhat less immunity to intercurrent disease than the normal. With a view to obtaining information of the effect of insulin therapy on them we have accepted every opportunity to study cases with complications. Minor maladies, such as colds or mild bronchitis, which ordinarily continue for weeks in the average diabetic, are often seen to clear up with great rapidity on adequate insulin therapy. In diabetes, associated with advanced pulmonary tuberculosis, the use of insulin has made it

possible for the patient to be supplied a diet far in excess of the necessary amount for the maintenance of life, and thus improves the outlook from the standpoint of the pulmonary disease. The pyogenic infections in diabetes, as is well known, usually clear up rapidly once the blood sugar is reduced to the normal level. When this cannot be done by dietetic measures alone insulin is necessary. Its continued administration, however, is in some cases by no means essential, as the extreme loss of tolerance for carbohydrate is often only temporary. With the clearing up of the infection, after a period of rest to the pancreas by insulin treatment, a partial or complete restoration of the tolerance may result and insulin may be discontinued.

Operative interference in the diabetic up to 1914 was attended with about 70 per cent. mortality. This was due mainly to the fear of operation and consequent delay until the condition became hopeless. During recent years, when the importance of adequate dietetic treatment has been more generally recognized, and a larger number of necessary operation procedures have been undertaken at an earlier period, the mortality has been much less. It has previously been our custom to advise operation in all urgent cases which could be made sugar and acetone free. Operation in certain other cases has been carried out because of necessity.

With insulin we no longer fear to advise operation on account of the diabetic condition. Each individual case must be carefully considered, and the possible benefits and possible dangers to the patient carefully weighed. If, then, it seems advisable to institute surgical proceedings with a reasonable chance of benefit to the patient we are inclined to use insulin in addition to ordinary dietetic measures, even though the latter suffice to make the patient aglycosuric and free from ketones. A liver full of glycogen undoubtedly prevents or reduces to a minimum the danger of post-operative acidosis. We, therefore, increase the carbohydrate above the patient's tolerance and use insulin to prevent glycosuria and to store glycogen. Tonsils, amputations, appendicial abscess and prostatic adenomas have been successfully operated upon in this way. In several cases dental operations of considerable magnitude have been successfully performed.

A remarkable fact, repeatedly observed, is the high tolerance for insulin during septic conditions, particularly seen in moist

gangrenes or infective cellulitis of the leg. In part this is certainly due to the accompanying acidosis such cases usually display, but it is not impossible that we are here dealing with an additional factor, possibly the rapid breakdown of body protein and consequent increased requirement of insulin for its metabolism, as well as the well known loss of tolerance for carbohydrates seen during infections. Coincident with the healing of such a pyogenic infection there is a reduction in the insulin requirement of the patient.

The behavior of the acetone bodies under the influence of insulin is being treated in a separate paper.[4] Examination of the protocols given in this paper will serve to show the results of insulin therapy on the milder degrees of ketosis. In general it may be said that, given sufficient carbohydrate intake, all degrees of ketonuria may be restored to normal by insulin administration. The requirement of insulin is much higher than is associated with the combustion of sufficient carbohydrate to avoid the development of a ketosis, and dosage must be gauged accordingly.

It was generally anticipated that difficulties would arise in the after care of patients under insulin treatment but these have not been as great as might have been expected. Certain cases present individual problems which are usually recognized during their stay of six weeks or more in hospital. Without this preliminary hospital control these difficulties without doubt would have been much greater. While in the clinic the patient learns the limitations and dangers of the treatment as well as its benefits. He is given an opportunity to appreciate food values and the importance of weighed diets. He experiences the occurrence of hypoglycemia and knows how to recognize its onset and how to treat it. When he has been once free of glycosuria for some time on an adequate diet he is not likely to tolerate its reappearance with the indifference so often seen in the discouraged diabetic. While in the hospital the proper adjustment of dosage is determined, and its proper spacing and timing. Patients are taught to administer the insulin themselves and appear to have had no mishap as a result. Mothers and nurses have administered the insulin to children. We have maintained a measure of control upon the amount of insulin which is allowed to any one patient and, in this way, have avoided the danger of the patient gradually attaining a precarious level of high diets and high dosage of insulin. We have been in frequent communication with dis-

charged patients living at some distance from a hospital centre or their family physician. These patients make daily examinations of their urine, administer the insulin themselves and, up to the present time, have not encountered any special difficulty in continuing their treatment. It is usually possible to adjust the time of dosage of insulin so as not to interfere with the usual routine of their occupation. In other cases the laboratory examination and the dietetic control, etc., have been carried out under the direction of the family physician.

Conclusions: Further evidence is offered in support of the conclusions reached in our previous papers and noted in the introduction to this paper. The clinical histories and protocols of a number of severe diabetics are presented and interesting features of their treatment discussed. Suggestions are made as to the criteria on which to judge the requirement of insulin in various cases, and as to the mode of treatment to be adopted. Our present position on a number of problems of metabolism made possible of solution by the introduction of insulin into the clinical treatment of diabetes mellitus is indicated in the discussion of the cases presented. At this stage, when no case has been under continuous treatment for a year, it is too early to prognosticate remote results of insulin treatment. Such evidence as we have indicates that a satisfying degree of control of the disease may be maintained even after the patients have left the hospital and there is no room to believe that this will not continue. Indeed it may not unreasonably be expected that the more rigid obedience to the regimen necessary under insulin treatment will prove of positive benefit to patients otherwise inclined to be some what lax in their dietetic treatment.

To Dr. Duncan Graham, Professor of Medicine, we wish to express our thanks for his constant interest and supervision in the conduct of these investigations. We beg to acknowledge the valuable assistance given us in this work by Dr. K. Murray, House Physician. To Misses Ratz, Lang and McPherson we are indebted for much assistance in carrying out the chemical examinations on the cases investigated.

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KETOSIS, ACIDOSIS AND COMA TREATED BY INSULIN

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The total glucose in the diet has a double duty to perform in that, besides furnishing energy during its oxidation, it is also essential in the complete oxidation of fats. This phase of its usefulness has been well discussed recently by Woodyatt,[7] Wilder[6] and Shaffer[5] and apparently the conclusion to be drawn, if the underlying hypotheses are correct, is that the fats are burned in the proportion of one molecule of fatty acid to one molecule of glucose except when the additional calories required, or fat supplied, is high, when a 2:1 molecular ratio may hold. From a clinical standpoint this seems to be true in the large majority of cases of diabetes mellitus but apparently does not hold for a few cases, particularly those associated with pregnancy.

The concept, however, has proven most useful in calculating a suitable diet for the diabetic. In these cases it is all important to provide pancreatic rest, and the use of fats to spare the islet tissue from over-strain due to excessive protein and carbohydrate metabolism is fundamentally important. When a large part of the power to burn glucose is lost the maximal calories will be supplied with the least strain by making use of the information gained from the work of the above mentioned writers to provide maximal energy from the fat in the diet. Diets may be improperly balanced; excessive amounts of glucose or protein may be consumed overworking the islet tissue of the pancreas; defective combustion of these substances may ensue, or excessive amounts of fats may be eaten or mobilized due to an abnormal energy requirement or other causes, or infection may severely impair the insulin production by the islets either temporarily or permanently, and thus the ratio of burning fat and total glucose may become unsuitable. Under such circumstances among others, the production of the acetone bodies, acetone, acetoacetic acid and

B-oxybutyric acid may occur. These substances have an intoxicating, then anesthetizing effect on the tissue. In addition the acids use up the bases of the body in an effort to neutralize them and, finally, materially alter the hydrogen ion concentration. There seems to be some clinical evidence that an actual irreversible alteration in the body tissues goes on from which the patients do not recover.

When the amounts of acetone bodies produced are small the mineral salts absorbed in the diet, or even the amount of fluid taken may be sufficient to permit of their excreton in the urine without causing any symptoms. This condition may be called simple ketosis, and usually can be successfully treated by a slight readjustment of the diet. With a larger production of ketones, the increased demand for base to neutralize these causes a deficiency in the available alkali and a condition of acidosis results. If the rate of excretion be insufficient these ketones continue to accumulate in the body and the patient proceeds into coma.

The occurrence of simple ketosis is usually not of much importance in the clinical aspects of the case but the severer degrees have a very serious import. In a preliminary paper[1] of March, 1922, we noted that ketonuria could be abolished by administration of pancreatic extract. The rather striking success we found in our early cases led to the opinion that more severe degrees of the condition, acidosis and coma, might possibly be benefited. Our next patient was a young girl with very severe diabetes and marked acidosis which improved remarkably on injections of the extract. The severity of the condition was such, however, that she needed continuous injections of insulin, and this was impossible to provide at the time. The patient went into coma and was brought out by using large quantities of a very weak, partially prepared extract, but she relapsed into a state of acidosis and died in coma, when no extract was available. Though with a fatal outcome, we now felt confident that extract, administered in sufficient dosage, would cure coma.

In view of these results it seemed of value to investigate the mechanism of the relief of ketosis in its various degrees with insulin, and find, if possible, a suitable method of handling such cases. The cases showing lesser degrees of the condition on admission often clear up readily on dietetic treatment alone as the glycosuria decreases but, if not, the acetone body excretion is rapidly cleared when insulin is added to the treatment, and the patient becomes aglycosuric. Several examples of this occur in

the preceding paper,* where the methods used in the chemical investigation of all these cases may also be found.

The question whether insulin alone has any specific influence on the metabolism of fatty acids is a very difficult one to settle and, in fact, the results we at present possess are open to either interpretation. Though, in the early work, with very dilute extracts no demonstrable result was obtained, other instances like the following occur.

A patient of 11 years, weight 72½ lb., height 4 ft. 10 in., was given a diet of protein 32 gm., fat 123 gm., carbohydrate 35 gm., calories 1375, on which she became aglycosuric in seven days, the blood sugar falling to normal and the ketone bodies in the urine averaging 1298 mg. per 24 hours. On a diet of protein 32 gm., fat 143 gm., and carbohydrate 38 gm., calories 1576, the patient remained aglycosuric; the ketone bodies in the urine averaged 1279 mg. per 24 hours but the blood sugar gradually rose to .148 per cent. Insulin was then given in doses of 5 units twice daily with a fall in blood sugar to normal and in the ketone body excretion to 1000 mg. per 24 hours. This apparently demonstrates a fall of 20 per cent. in ketone body excretion, but it may be pointed out that there was an associated fall in the blood and probably tissue sugar which might account for the burning of the ketones. The diet was then increased by 5 gm. of carbohydrates and 20 gm. of fat, the dose of insulin remaining the same, and the acetone body excretion fell to an average value of 695 mg. per day, a somewhat greater fall than was noted before, and the blood sugar rose to .12 per cent. When we consider the other factors which are also involved, it seems probable that the reduction in ketone bodies seen here must be associated with increased combustion of carbohydrate or carbohydrate derivatives.

The effect of a single dose of insulin on the acetone bodies of the blood and urine, when adequate carbohydrate is available, is illustrated by the following two cases:

Case 1—The patient was a severe diabetic of fifty years, who, on a basal diet of protein 37 gm., fat 134 gm., crabohydrate 38.5 gm., was excreting approximately 6 gm. of sugar and considerable amounts of ketone bodies. On the first day (control day) the patient took his regular meals at 8 a.m., 12 noon, and 5 p.m. The urine was collected at intervals and examined. At the same time the blood was taken for examination of blood sugar and ketone body contents. The second day (test day), one day following the control day, differed from it only in the administration of 40 units of insulin on the excretion of ketone bodies in the urine is seen in Table I, comparative basis, maximal intensity of reaction being indicated by 4. The control day shows the fall in acetone bodies in the blood as well as a slight fall in the blood sugar, which may possibly be attributed to the stimulus to insulin mobilization as a result of meals and consequent combustion of carbohydrates and ketones. The effect of a single dose of insulin on the excretion of ketone bodies in the urine is seen in Table I,

*This journal.

but is perhaps more striking if the results are recalculated as mg. per hour excreted, as follows: 80, 36, 0, 48, 54, 28. There is an indication here of immediate combustion of the ketones when insulin is introduced and the result appears to occur quite as promptly as the reduction in blood sugar. The same result has been obtained in the majority of cases we have examined.

TABLE I

Time	Urine					Blood	
	Vol. c.c.	Sug. Gm.	Ketone Bodies			Sug. %	Ketone Bodies Mg. per 100 c.c.
			SNP	$FeCl_3$	Mg.		
Control day							
6–8*.....	90	1.33	3	2	....	.231	26.5
8–10.30*.....	310	1.49	3	1	....	.235	
10.30–12*.....	310	.25	3	3	....	.196	7.38
12–3*.....	320	.50	2	0	2190	.245	
3–6*.....	230	2.05	3	2	....	.223	21.8
6–6.....	930	9.49	3	2	....		
Intervening day							
6–6.....	2530	1.7	3	1	2783		
Test day							
6–8*.....	280	1.93	3	1	160	.195	
8–10.30*.....	910	0	2	0	54	.163	
10.30–12*.....	500	0	0	0	0	.139	3.41
12–3*.....	600	0	2	0	146	.143	
3–6*.....	520	0	2	0	164	.104	4.48
6–6*.....	1100	.72	3	3	341		
Following day							
6–6.....	2800	15.1	3	1	2873	.210	

*Time of taking blood for analysis.

Case 2—The patient was a youth of twenty years, perfectly well 2½ years ago. Noticed first, thirst and polyuria, then that he became very much fatigued on light work. Has been on a diet limited as to kinds of foods but states he has eaten twice as much as a normal person would eat. Has lost 10 lb. in weight in the past two years. On a diet of protein 32 gm., fat 126 gm., carbohydrate 33 gm. he excreted 14 gm. of carbohydrate and 4-10 gm. of acetone bodies daily—no blood ketone bodies were estimated. The control day differs from the test day in that 30 units of insulin were given at 8 a.m. on the test day. Though there seemed no reason to suggest that diet might be a factor in these results, case 2 was fed non-nutrient substances for breakfast on the test day and control day. The results are similar to those in case 1. (Cf. Table II.)

Acidosis

Though a large percentage of cases of severe acidosis may be adequately treated by dietetic means, one nevertheless sees cases which progress steadily into coma in spite of all previous methods of treatment. In the three following tables is summar-

ized the treatment of three cases of acidosis in diabetes mellitus of sufficient severity to make their subsequent course under any other treatment at least very doubtful. These patients showed a prompt disappearance of acetone bodies from the blood and urine with a coincident rise in the CO_2 combining power of the blood and improvement in the general clinical condition of the patient. Glucose was given in association with the insulin to prevent the occurrence of hypoglycemia.

L.F.—Aet. 15; Canadian; admitted January 15, 1923; best weight 100 lb.; present weight 79 lb.

First noticed thirst, polyuria and weakness in November, 1921. Had scarlet fever twelve months ago and at that time glycosuria was discovered. A diet was prescribed, on which thirst and polyuria decreased but he gradually became weaker.

Past Illnesses: Measles, whooping cough, chickenpox in infancy, scarlet fever, December, 1921.

Family history: Negative for diabetes.

Examination: Young, thin boy, 5 ft. 3 in. tall, depressed, weak, inactive mentally and physically. Tongue rather dry, skin dry and harsh. Acetone

TABLE II

Time	Urine					Blood Sugar %
	Vol. c.c.	Sug. Gm.	Ketone Bodies			
			SNP	$FeCl_3$	Mg.	
Control day						
7– 8*	240	.9	2	1	383	.192
8– 9*	40	.3	2	1	100	.205
9–10*	115	.14	2	1	260	.210
10–11*	90	.3	2	1	38	.217
11–12*	90	0	2	1	101	.174
12– 7	1180	2 71	2	1	1085	....
T st day						
7– 8*	220	0	1	1	65	.171
8– 9	132	0	1	1	25	....
9–10	85	0	1	0	21	....
10–11*	280	0	0	0	0	.102
11–12*	305	0	0	0	0	.077
1*	....	....	....	....	....	.083
2*	....	....	....	....	....	.079
12– 7	1480	0	1	0	1070	....

*Denotes time of taking blood for analysis.

on breath. Breathing rapid and prolonged. Otherwise the physical examination showed no departure from normal. (Cf. Table III.)

M.K.—Aet. 43; Canadian; school teacher; admitted January 5, 1923; best weight 120 lb.; present weight 64 lb.

Has noticed progressive loss of weight for the past eleven years, with increasing lassitude and loss of strength. Nine years ago polydipsia,

TABLE III

Time	Urine						Blood				Alv. CO_2 mm.	Insulin	
	Vol. c.c.	Sp. G.	Sug. Gm.	Rothera Test	$FeCl_3$ Test	Acetone Bodies Mg.	Time	Sug. %	Ketones Mg. per 100 c.c.	CO_2 Comb. Power		Time	Units
15/1/23													
7 a.m.–7 p.m.	1400	10 30	88	4	3	7551	4.00 a.m.	.325					
16/1/23													
7 a.m.–12 n.	700	10 38	42.2	3	3	3800							
12 n.–4 p.m.	175	....	6.7	3	3	1880	4.00 p.m.	.334	82	15.9	23	4.15 p.m.	40
4 p.m.–8 p.m.	25	....	0	3	2	675	8.00 p.m.	.185	57.5	31	42	8.00 p.m.	20
8 p.m.–12 m.	55	10 25	0	3	2	50	12 m.	.164	35.4	38.4	40	12 m.	20
17/1/23							4.00 a.m.	.097	27	43	38	4.00 a.m.	20
12 m.–8 a.m.	300	10 25	0	3	1	166	8.00 a.m.	.102	22	42	40	8.00 a.m.	20
8 a.m.–12 n.	70	....	.26	3	2	32	12 n.	.110	34.6	53	38	12 n.	20
12 n.–4 p.m.	315	....	.25	2	1	76	4.00 p.m.	.117	12.6	49	38	4.00 p.m.	20
4 p.m.–8 p.m.	100	10 10	....	2	1	20	8.00 p.m.	.126	15.6	52	40	8.00 p.m.	20
8 p.m.–12 m.	260	10 15	....	2	1	25							
18/1/23													
12 m.–4 a.m.	320	....	.77	0	0	0	4.00 a.m.	.146	15.5	46	30	4.00 a.m.	20
4 a.m.–8 a.m.	320	....	0	2	1	105	8.00 a.m.	.129	6.01	54	38	8 00 a.m.	20
8 a.m.–12 n.	260	....	0	0	0	0	12.00 n.	.105	5.55	53	38	12.00 n.	20
12 n.–4 p.m.	520	....	0	0	0	0	4.00 p.m.	.129	0	54	38	4.00 p.m.	20

Patient received 20 gm. glucose with 200 c.c. water, by mouth, with each dose of insulin except the first.

polyuria and puritus developed and she consulted a physician, who found glycosuria. In 1916 she was in hospital and aglycosuric on a low calorie, low carbohydrate diet and remained on the diet for three months. She gradually resumed a normal diet, though she has been eating to excess during the past three years.

Past illnesses: Measles, mumps, pyorrhea.

Family history: Father died of apoplexy; one brother died of diabetes mellitus; one brother has diabetes mellitus.

Examination. Markedly emaciated, sallow, wrinkled woman. Skin dry. Some edema of feet. Teeth removed. Throat normal. Tonsils not seen. General atonic kyphosis. Muscles wasted and atonic. Circulation—heart normal; pulse regular, small volume; slight thickening of vessel walls; B.P. 96/60. Respiratory system—subject to nasal infections, otherwise normal. Gastro-intestinal system—normal. G.U. system—pruritus vulvae; frequency; polyuria. Nervous system—cutaneous reflexes easily obtained; deep reflexes difficult to obtain. (Cf. Table IV.)

R.K.—Aet. 35; housekeeper; admitted January 17, 1923.

Four years ago patient developed polydipsia and polyuria. Three years ago her appetite became excessive. Pruritus vulvae developed two years ago. Is six months pregnant; attended pre-natal clinic and was admitted to hospital because of glycosuria. The following day she was transferred to the diabetic ward because of difficult, painful breathing and acetone odor on the breath. Has never been on a regulated diet.

Past illnesses: Sore throat in childhood, influenza in 1918.

Family history: One brother died with diabetes; one sister died with diabetes.

Physical examination: Adult Jewess, extremely dyspneic, pale; acetone on breath; thyroid very large and adenomatous, no toxic signs.

Circulation: Heart not enlarged, sounds good quality; vessels not thickened; pulse regular, good volume.

Respiratory system: Nothing abnormal found.

Digestive system: Nothing abnormal found.

Genito-urinary system: Six months pregnant.

Nervous system: Reflexes easily elicited, equal and normal responses. (Cf. Table V.)

The third case, R.K., is somewhat different from the two preceding cases in that the acidosis of diabetes was complicated by pregnancy. The blood sugar and blood acetone bodies were close to normal limits for the last 16 hours, and the sugar excretion was low and acetone bodies absent from the urine during the last 12 hours. The clinical condition of the patient improved with the removal of the ketones, but the CO_2 combining power of the plasma and the alveolar CO_2 remained at very low levels. Some decrease in the CO_2 combining power of the plasma during pregnancy was noted by Losee and Van Slyke.[3] Hasselbalch and Gammeltoft[2] had previously noted an alveolar CO_2 lower than normal during the later months of pregancy. Values as low as in

TABLE IV

Time	Urine						Blood				Alv. CO_2	Insulin	
	Vol. c.c.	Sp. G.	Sug. Gm.	Ketones SNP	Ketones $FeCl_3$	Ketones Mg.	Time	Sug. %	CO_2 Comb. Power	Acetone Mg. Per 100 c.c.		Time	Units
5/1/23													
7.00 p. m.– 7.00 a. m.	700	1036	34.3	3	3	2215	4.00 p. m.	.465	....	49	27	.....	....
6/1/23													
7.00 a. m.– 9.00 a. m.	280	1038	13.5	3	2	600	8.00 a. m.	.295	45	....	30	8.00 a. m.	40
9.00 a. m.–11.00 a. m.	120	1035	5.75	3	2	106	10.00 a. m.	....	....	....	33	.....	....
11.00 a. m.– 1.00 p. m.	140	1036	7.7	3	2	191	12.00 a. m.	....	....	....	30	11.00 a. m.	40
1.00 p. m.– 3.00 p. m.	300	1008	0	2	0	61	2.00 p. m.	....	....	....	32	3.00 p. m.	40
3.00 p. m.– 5.00 p. m.	300	1005	0.27	2	0	625	4.00 p. m.	....	....	....	32	.....	....
5.00 p. m.– 7.00 p. m.	160	1013	2.2	3	1	93	6.00 p. m.	....	....	....	30	6.00 p. m.	20
7.00 p. m.– 9.00 p. m.	120	1016	2.7	2	1	505	.....	....	....	....	....	9.00 p. m.	20
9.00 p. m.–11.00 p. m.	320	1006	2.4	1	0	0	.....	....	....	....	....	12.00 m.	20
11.00 p. m.– 7.00 a. m.	430	1007	.52	0	0	0	.....	....	....	....	....	3.00 a. m.	20
												6.00 a. m.	20
7/1/23													
7.00 a. m.–12.00 n.	625	1006	0	0	0	0	9.00 a. m.	.054	55.5	2.16	....	.....	....
12.00 n. – 2.00 p. m.	500	1006	0	0	0	0	.....	....	....	....	....	.....	....

Glucose 20 gm., with water 200 c.c., by mouth with each dose of insulin.

TABLE V

Date—Time	Urine						Blood				Alv. CO_2 m.m.	Insulin		Remarks
	Vol. c.c.	Sp. G.	Sug. Gm.	SNP	FeCl3	Ketones Mg.	Time	Sug. %	CO_2 Comb. Power	Ketones Mg. per 100 cc.		Time	Units	
19/1/23														
4.00 p.m.			++	3	2		4.00 p.m.	.20		62	18—	4.00 p.m.	40	Glucose 20 gm. with each insulin injection.
4-8.00 p.m.	215	1020	7	3	2	1725	8.00 p.m.	.161	24	44.1	19	8.00 p.m.	20	
8-12.00 n.	225	1017		3	2		12.00 m.	.155	24	29 8	17	12.00 n.	20	
20/1/23														
12-4.00 a.m.	185	1020	1 .85	3	1	189	4.00 a.m.	.186	12	15 5	22	4.00 a.m.	20	Plasma for CO_2 contains Hb.
4-8.00 a.m.	120	1027	2 .0	3	1	109	8.00 a.m.	.166	33	15 .8	22	8.00 a.m.	20	
8-12.00 m.	205	1020	1 .58	3	1	254	12.00 n.	.167	33	17 .8	20	12.00 m.	20	
12-4.00 p.m.	320	1013	2 .69	2	1	115	4.00 p.m.	.194	31	18 .9	24	4.00 p.m.	30	
4-8.00 p.m.	240	1020	2 .76	2	1	97	8.00 p.m.	.202	31	8 0	22	8.00 p.m.	30	
8-12.00 n.	146	1021	1 .3	2	0	32	12.00 n.	.152	38	1 .6	22	12.00 n.	30	
21/1/23														
12-4.00 a.m.	130	1019	1 1	0	0	0	4.00 a.m.	.123	39	2 .13	25	4.00 a.m.	30	
4-8.00 a.m.	140	1016	.91	0	0	0	8.00 a.m.	091	38	0 45	25	8.00 a.m.	30	
8-12.00 n.	690	1003	0	0	0	0	12.00 m.	.089	39	1 .28	26	12.00 n.	30	

this case do not occur in their reports. Several possibilities presented themselves:

(1) Sudden release of base through combustion of the ketones in the blood and tissues, when the store of CO_2 had been driven off by an hyperpnea associated with the acidosis, might produce a relative alkalosis and loss of base in the urine or neutralization of the base by migration of HCl from the corpuscles. This seemed unlikely, however, as the combustion of the ketones themselves would yield more than sufficient CO_2 to combine with the base and, further, the urine was always acid to litmus; (2) The patient was suffering from a toxemia of pregancy with an acidosis partly other than ketonic in origin. This is unlikely, as the patient presented no other symptoms of the pregnancy toxemia; (3) Another possibility was that the low alkali reserve was occasioned by a continuous loss of base by excretion, or insufficient intake of bases in the food. Though a certain amount of the ketosis may have been due to the pregnancy, Harding has shown that, given sufficient carbohydrate, the ketosis of pregnancy clears up rapidly. The last possibility seems a most likely one.

An attempt was then made to replace the mineral loss of the body by feeding a mixture of salts as follows, every four hours: Sod. chloride, 10 gm.; Pot. chloride, 3 gm.; Sod. bicarb., 8 gm.; Calcium chloride, 1 gm.; Magnesium carbonate, 3 gm. This mixture was somewhat nauseating and caused slight diarrhea and, combined with a decrease in the dose of insulin, there was an increase of acetone bodies in the blood and urine. A well marked rise in the alkali reserve occurred. However, there is no evidence to show that this was due to anything other than the bicarbonate in the mixture. Table VI gives the chemical results following the use of the salt mixture.

In the brief reports given above there seems to be sufficient evidence that, except in the case R.K. presenting a decreased combining power for CO_2 from causes other than neutralization with the acetone bodies,, insulin, in combination with sufficient carbohydrate, causes combustion of the ketones with a very satisfactory measure of relief of the acidosis from the clinical standpoint. The ketone bodies decrease markedly or disappear from the blood and urine, and the CO_2 combining power of the blood and the alveolar CO_2 return to the lower limit of normal. If one wished to stress the point, there might be calculated a direct relationship between the amount of ketones burned and the

TABLE VI

Date—Time	Urine						Blood				Alv. CO_2	Insulin		Remarks
	Vol. c.c.	Sp. G.	Sug. Gm.	SNP	$FeCl_3$	Ketones Mg.	Time	Sug. % Mg.	CO_2 Comb. Power	Ketones Mg. per 100 c.c.		Time	Units	
21/1/23														
12–4 p.m. ..	1015	10 01	0	0	0	0	4.00 p.m.	121	38 3	6 .65	28			Salt mixture q. 4 h.
4–8 p.m.	340	10 17	0	1	0	156	8.00 p.m.	110	39 .3	18 .6	28	8.00 p.m.	10	
8–12 m.	250	10 14	0	3	0	205	12.00 m.	089	45	13 7	28			Vomited small amount.
22/1/23														
12–4 a.m. ..	340	10 20	0	3	1	581	4.00 a.m.	119	40	38 .5	22			
4–8 a.m.	400	10 19	.36	3	2	1815	8.00 a.m.	126	40	42	25	8.00 a.m.	20	
8–8 a.m. ..	2180	10 16	0	2	1	3894	8.00 a.m.	07	56 .5	16	33	12.00 n.	20	
23/1/23							23/1					6.00 p.m.	20	Salt mixture discontinued.
												6.00 a.m.	20	
23/1/23	3200	10 09	0	1	0	913	9.00 a.m.	083	52	10 3	33	12.00 n.	20	
24/1/23							24/1					6.00 p.m.	20	
												12.00 m.	20	
24/1/23	1670	10 06	0	?	0		9.00 a.m.	08	54	3 .51	34	6.00 a.m.	20	
25/1/23							25/1					12.00 n.	20	
												6.00 p.m.	20	
												12.00 m.	20	
25/1/23	3350	10 09	0	?	0		9.00 a.m.	09	51		35	6.00 a.m.	20	
26/1/23							26/1					12.00 n.	20	
												6.00 p.m.	20	
												12.00 m.	20	
26/1/23	4440	10 09	0	0	0	0	27 1	076	50	0	40			
27/1/23														

amount of base released for combining with CO_2 in some instances, but other factors besides the direct neutralization power of the acids and alkalies are undoubtedly concerned in this mechanism, which would make such a calculation open to question. Case L.F. is, from a chemical standpoint, one of very severe acidosis and, indeed, patients are found in coma with less severe derangement of metabolism. It responded in an ideal manner to the administration of insulin and carbohydrate. Case M.K. is less severe from a chemical standpoint, but marked emaciation and acidosis, even of a comparatively slight degree, is a very serious clinical condition. The response in this case is also satisfactory. The third case is somewhat different and, though the ketones are burned, the CO_2 combining power, or available alkali, remains decidedly below the level common either in diabetes or in pregnancy. It responded satisfactorily to a combination of insulin, carbohydrate and a mixture of mineral salts, including alkali.

Coma

Notwithstanding its value in the lesser degrees of derangement of fat metabolism, the most striking benefit of insulin is seen in its relief of diabetic coma. It is unnecessary to dilate upon the prognosis in these cases under former methods of treatment, as it is well known that the large majority have been regarded as hopeless. Since commencing insulin treatment fourteen cases of diabetic coma have entered the clinic. Seven are now living, most of them on a diet with insulin but some without insulin, though still under dietetic treatment. With the exception of the first case noted above, and one other noted hereafter, all those who have died have had an associated infection sufficiently severe to result fatally apart from the diabetic condition. One of these died from the toxic effects of a sloughing gangrenous foot ten days after being brought out of coma; three had pneumonia and one pyemic abscesses in the kidney. In all but one case, where perhaps insufficient insulin was used, the comatose condition in all the fatal cases was improved clinically and chemically.

In the guidance of treatment of this condition a considerable amount is left to one's clinical judgment, as most of the laboratory tests are too time consuming to be of much immediate value. The estimation of the CO_2 combining power of the blood at intervals, the Rothera test on the plasma, and examination of the urine for sugar and ketones have been useful. No suitable method has

been found for the estimation of the alveolar air of comatose patients, and all our results have been somewhat irregular, and might have been misleading at times. As one might expect on *a priori* grounds, the first signs of improvement are clinical in nature and consist in decrease in the depth of the coma shown by resumption of movement, irregular, purposeless and uncoordinated at first, later voluntary response to painful or disagreeable stimuli, response to commands, then compliance with them, later, recognition of people and evidence of thought. With these go the reduction in blood ketones and rise in the CO_2 combining power of the blood. The blood sugar percentage is necessarily variable on account of the time of administration of the glucose and of the insulin. The following case reports illustrate some of the results of treatment and interesting facts observed.

W.M., aet. 30; weight 122 lb.; best weight 177 lb.; admitted October 6, 1922.

Until August, 1921, was quite well. An intense thirst developed at this time, with polyuria and loss of weight. In October, 1921, consulted a physician who treated him after Allen's method and raised his diet gradually to protein 80 gm., fat 90 gm., carbohydrate 40 gm., calories 1290. He became free of symptoms. He gradually increased the quantities of food allowed and in July symptoms returned and have increased in severity.

Previous illnesses: None.

Family history: Negative for diabetes.

Examination: Well developed, adult male, emanciated, markedly dehydrated; skin dry and scaly; slight varicosity of right leg veins; peridental infection; acetone on breath. Reflexes sluggish. Well-marked anemia; R.B.C. 3,200,000; B.P. 112/78. Otherwise nothing of note in the physical examination. He was placed on a diet of protein 38 gm., fat. 145 gm., carbohydrate 39 gm., calories 1613, and fluids were given liberally. The glycosuria decreased and with it the polyuria but acetone was detectable on the breath almost continuously. On October 11 the breathing became more prolonged and he refused supper because of nausea. He vomited twice the next morning and became very drowsy and weak. Tongue thick and crusted. Respirations increased in rate and depth. He gradually became difficult to rouse and speech became difficult.

Treatment: As the patient was not completely comatose, a smaller quantity of insulin than usual—40 units—was given intravenously. The clinical condition of the patient did not improve. He became more comatose. Uncontrolled, purposeless movements of the hands and legs were present, and he did not respond to commands, though he would still swallow when fluid was placed in the mouth. At 2 p.m. 120 units of insulin and 100 gm. of glucose were given intravenously. As will be seen by examination of Table VII, there was chemical evidence of improvement even at this time in the rising CO_2 combining power of the plasma and decrease of the ketones in the blood, The subsequent rapid clinical im-

provement in his condition, which began to be noticeable within an hour, cannot, therefore, be wholly attributed to the effect of the second dose of insulin. The patient became more rational and attempted to vomit several times. It is thought, however, that he retained the larger part of the fluids given. The breathing became less deep and the patient said that he felt better. Headache gradually disappeared. At 11 p.m. a marked decrease in the intensity of the ferric chloride reaction in the urine was noticeable and the patient was given 40 units more insulin at 12 midnight, and the nurses given directions to continue the administration of fluids containing sugar and fruit juices during the night. Next morning his condition was good; deep breathing and acetone on the breath absent, and he stated that he felt well but still rather weak. Subsequently the patient was replaced on his original diet. For a considerable period he required very large amounts of insulin in order to keep the urine free of sugar, but there has been gradual reduction in the requirements and he now is receiving 40 units in the day—8 a.m. 20 units, 1 p.m. 10 units and 8 p.m. 10 units. He is aglycosuric and free from acetone. Blood sugar remains about 0.1 per cent.

Examination of Table VII shows the results of treatment from a chemical standpoint. The blood sugar, of course, remained high as was intended in order to protect against hypoglycemia. The CO_2 combining power of the plasma rose steadily, though not rapidly, to the lower limit of normal on the 14th. There was, however, some delay in the rise after 9.30 p.m. on the 12th of October. No alkali was given in this case and any mineral salts obtained were derived from the lemon and grape juice used to flavor the sugar solutions given by mouth. The rise in the CO_2 combining power after 11.15 a.m., October 13th, is equivalent to setting free 18 gm. of sodium bicarbonate[4] in the body. As the blood acetone bodies remained the same, the source of this alkali remains unexplained. The ketones in the blood rapidly fell to safe levels though, on the previous day, 30 gm. of total acetone bodies were excreted, and the patient was becoming progressively worse on liberal fluid administration. The total acetone body excretion for this day was about 13 gm., of which 12 gm. were excreted before the second intravenous injection of insulin was completed.

M.T., aet. 24; height 5 feet; weight 78 lb.; admitted to hospital, December 18, 1922.

In 1917 patient noticed abnormal appetite, thirst, polyuria and loss of weight. She knew the cause as several relatives had diabetes, but did not consult a physician until 2 years ago. During this time the symptoms were increasing in severity. The diet prescribed allowed her to be sugar free at intervals. Later she visited a large clinic and was made sugar free on a diet of 1100 calories containing 20 gm. of protein and 10 gm. carbo-

TABLE VII

Date Time	Urine						Blood			Insulin			Remarks
	Vol. c.c.	Sp. G.	Sug Gm.	Ketones			Time	Sug. %	CO_2 Comb. Power	Ketones Mg per 100 c.c	Time	Units	
				SNP	$FeCl_3$	Mg.							
10/10	1810	1027	42	3	2	16,817	11 00	.294	....	...	.....	...	Acetone on breath.
11/10	3200	1020	41	3	3	30,554	.....	....	....	...	.....	...	Prolonged breathing.
12/10	....	....	....	...	...	.....	.....	....	....	...	.....	...	
7 – 9	250	1016	3 75	3	3	2,221	10.00	431	16.6	111	10.00 a. m.	40	1000 c.c. 10% glucose intravenously.
9 – 3	1490	1020	33	3	3	9,703	1.00	.395	20.4	93	2.00 p. m.	120	1000 c.c. 10% glucose intravenously.
3 – 5	140	1023	4.9	3	2	339	....	....	....	...	.....	...	
5 –11	720	1021	18	2	1	648	9.30	.515	34 7	55	.....	...	Vomiting.
11– 3	390	1024	10	1	0	99	.....	....	....	...	12.00 m.	40	
3 – 7	470	1028	9	1	0	244	.....	....	....	...	4.00 a. m.	40	Large quantities of fluids.
13/10	....	....	....	...	...	.....	.....	....	....	...	.....	...	
7 –11	420	1027	13	1	0	70	.....	....	....	...	8.00 a. m.	40	
11– 3	450	1012	10	0	0	.....	11.15	.452	37.6	6	12.00 n.	40	Respirations normal.
3 – 7	630	1009	2	0	0	.....	.....	....	....	...	4.00 p. m.	40	
7 –11	650	1006	2	0	0	.....	.....	....	....	...	.....	..	
11– 3	300	1006	6	0	0	.....	.....	....	....	...	12.00 m.	20	
3 – 7	300	1004	6	tr.	0	.....	3.15	....	49.4	7	4.00 a. m.	20	Condition good.
14/10	....	....	....	...	...	.....	.....	....	....	...	.....	...	
7 –11	390	1005	2	1	0	185	.....	....	....	...	8.00 a. m.	20	Taking fluids well.
11– 2	310	1005	2	0	0	.....	.....	....	....	...	.....	...	
2 – 7	550	1005	2.5	0	0	.....	.....	....	....	...	4.00 p. m.	20	
7 –11	400	1010	2	tr.	0	.....	.....	....	....	...	.....	...	
11– 3	300	1014	2	0	0	.....	.....	....	....	...	.....	...	
3 – 7	600	1006	4	tr.	0	.....	.....	....	....	...	.....	...	

hydrate. She has been sugar free half the time since, but very weak and not able to do any work.

Past illnesses: Three severe attacks of diarrhea of unknown cause; ordinary diseases of childhood; chronic otitis media.

Family history: Uncle has diabetes; father and sister died with diabetes.

Examination: No particular abnormality was noted on physical examination.

Treatment: The patient was treated on the usual plan, as outlined in the previous paper. On a basal diet of protein 24 gm., fat 90 gm., carbohydrate 26 gm., calories 1010, she excreted 34 gm. of sugar and considerable acetone. On non-nutrients no sugar was excreted, though the blood sugar was .3 per cent. and the acidosis was marked. On this day she had some pain and pus discharged from the left ear. No evidence of mastoid involvement. The following day the patient remained in bed. The glycosuria amounted to 33 gm. The patient was suffering considerable earache and considerable pus drained from the ear. In the afternoon the pulse and respiration rate increased. In the morning the patient ate her breakfast, omitting the fats. The pain in the ear was severe and much pus discharged. The pulse rate was high; respirations became deep, increased, labored and painful during the morning, and the patient, though quite bright in the early morning, later became quite drowsy and refused her dinner. Deep breathing was marked but she no longer complained of it. The ordinary methods of combating acidosis by rest, warmth and increased elimination had failed, and the patient was in imminent danger and, indeed, in the early stage of coma. It is unfortunate that the quantitative test for blood acetone at this time was overturned in the laboratory, but the CO_2 combining power—17.9, vols. per cent.—is sufficient evidence of the severity of the condition. Sixty units of insulin were given subcutaneously at 2 p.m. At 3 p.m. 10 gm. of glucose was given her by mouth with 200 c.c. of water. The patient's condition became very definitely worse in the next three hours. She gradually sank into a comatose state from which she could only be roused by vigorous shaking and could not articulate when roused. Ten gm. of glucose every hour were ordered, together with as much fluids as possible. 3400 c.c. of fluid were given in 24 hours. The volume of urine excreted shows the usual deficit occurring in coma. Forty units of insulin were given subcutaneously at 5.45 p.m. and subsequently the patient began to improve. At eight o'clock and thereafter she took the glucose and fluid offered her without difficulty, and at 10.45 p.m. made intelligent responses to questions, and it was judged at this time that 40 units more insulin would be sufficient to clear up the condition. The next morning she was quite bright but without appetite, though taking fluids greedily. Forty units of insulin were given subcutaneously at 10.40 a m. and repeated at 6.30 p. m. The patient ate no regular meals but took glucose and fluid regularly. In the afternoon she was definitely out of danger. The following day nausea developed from the glucose and this was reduced. The acetone bodies were practically negligible on this day. The following day the patient ate the larger portion of her regular diet and no acetone bodies were present in the urine.

The accompanying table (Table VIII) illustrates the progress of the

TABLE VIII

Date—Time	Urine						Blood				Insulin		Remarks
	Vol. c.c.	Sp. G.	Sug. Gm.	SNP	$FeCl_3$	Ketones Mg.	Time	Sug. %	CO_2 Comb. Power	Ketones Mg. per 100 c.c.	Time	Units	
19/12	1600	1027	9.2	2	1	10,791							
20/12	1000	1032	34.4	2	1	10,198	8.00 a.m.	.328					P. 24, F. 90, C. 26.
21/12	1300	1030	26.7	2	1	13,535	8.00 a.m.	.311					P. 23, F. 67, C. 26.
22/12	Specim	en lost											P. 24, F. 90, C. 25.
23/12	2550	1013	0	2	2		8.00 a.m.	.306	25.4	96			
							10.30	.359					Non-nutrients.
							12.00	.270	26.4	120			Discharge—left ear.
							3.00 p.m.	.337					
							6.00	.350	26.4	121			
24/12	4150	1010	33	2	2	15,987							P. 24, F. 90, C. 22.
													Ear discharging; drowsy.
25/12	2250	1010	8.	2	2	16,530	1.15	.421	17.9		2.00 p.m.	60	P. 36, F. 33, C. 92.
							5.15		10.3	75	5.45	40	Drowsy, deep breathing, coma.
							9.15	.193	29.3	44	10.45	40	Fluids 3410 c.c., glucose 156 gm.
							2.00 a.m.	.277					
26/12	2250	1010	26.1	1	?		8.00 a.m.	.307	35	14	10.10	40	Quite bright mentally.
											6.20	40	Glucose 200 gm.
											11.00 p.m.	40	
27/12	1550	1015	56	?	0	248	5.30 p.m.	.480		0	10.00 a.m.	20	Ear painful and discharging.
											1.00 p.m.	20	
											6.00	20	
28/12	1950	1015	42	0	0	0					8.00 a.m.	20	P. 23, F. 52, C. 44.
											12.00	20	Glucose 60 gm.
											5.00 p.m.	20	
29/12	2300	1010	62	1	0		1.00 p.m.	.492	57.5		12.00 n.	20	P. 21, F. 64, C. 28.
											5.00 p.m.	20	

case from the chemical point of view. The reduction in the CO_2 combining power of the plasma in the second specimen, taken at 5.15 on the 25th, is in accordance with the clinical condition. Apparently the blood acetones must have been decreasing as at this time they were distinctly less than two days previously. The subsequent improvement in the laboratory tests paralleled the clinical condition. This case shows the successful treatment of coma by subcutaneous injection of insulin after the methods commonly employed of decreasing acidosis—starvation and large amounts of fluid—had failed.

The otitis media gradually cleared up. The patient is now aglycosuric and has a normal blood sugar on a diet 700 calories above her basal requirement. Twenty units of insulin are being given twice daily before breakfast and before supper.

The two preceding cases illustrate the successful treatment of severe diabetic coma by the subcutaneous and intravenous administration of insulin.

The following fatal cases of diabetic coma, two of which had in addition an infection sufficiently severe to result fatally apart from the diabetic condition, are recorded. They present certain interesting and important facts which have a bearing on the use of insulin and on other points in the treatment of diabetic coma.

E.H., aet. 65; admitted in coma; died in 38 hours.

History of diabetes for four years. Dietetic regime not kept. Five days before admission, complained of nausea and pain in the back. These symptoms became less intense and patient gradually sank into a comatose condition. At time of admission to hospital, patient had been in a comatose condition for 60 hours. Admitted 12.30 p.m.

Examination: Well nourished woman, rather obese; high color; no cyanosis; breathing slow and irregular. Slight odor of acetone on the breath. Responds to stimulation; no paralysis; muscles hypotonic; reflexes could not be elicited. Eyes react to light but pupils are unequal. Skin dry; tongue dry; teeth missing. T. 99.6; P. 108; R. 12; B.P. 154/100.

Respiratory system: Markedly hyperresonant, except at the bases where there is some loss of audibility and harsh breath sounds with moist rales present Harsh breath sounds and rhonchi heard over whole chest.

Circulatory system: Vessels tortuous and markedly sclerosed; pulse good volume, regular with occasional dropped beats. Heart shows marked enlargement to left, 15.0 cm. from midline in 5th interspace; sound good quality; systolic murmur at apex. R. B. C.—5,120,000; W. B. C.—26,800.

Abdomen: Distended, no rigidity. Liver is enlarged and hard in consistency; point of tenderness in right mid-clavicular line below liver margin; palpation of this area causes spasm of the abdominal muscles. Kidneys and spleen could not be palpated.

Urinary examination: Urine was scanty; contained a large quantity of albumin, sugar and acetone, many pus cells, some blood and many casts were present. Although the urine showed a well marked Rothera nitroprusside reaction the ferric chloride tests gave a faint reaction indicating that only small quantities of diacetic acid were present.

In addition to the diabetic coma and fairly well marked cardiovascular disease this patient was suffering from a severe infection of the kidneys, as evidenced by fever, leucocytosis and the presence of albumin, blood, pus and casts in the urine.

Progress and Treatment: The patient was given 115.0 gm. of glucose and 120 units of insulin with 2300 c.c of fluid, injected intravenously in the course of an hour. The pulse improved in quality, decreased slightly in rate, but the patient became more comatose. 20 units of insulin were given every 2 hours. After the third injection of insulin the patient became brighter mentally, but became very restless and distressed on account of tympanites. This was relieved by passing the stomach tube and giving enemata. Throughout the night the patient's mental condition slowly improved. The pulse became quite irregular and was improved with digitalis and the further administration of intravenous glucose. The amount of fluids given otherwise was comparatively small. The next day the tympanites became very marked and was only partially relieved by pituitrin, physostigmine and enemata. The patient, however, recognized friends and talked rationally. Incontinence of urine and feces developed, but patient seemed in fair condition 36 hours after admission. Immediately after this greater difficulty was experienced in making her take fluids, and her respirations became slow and shallow. Improvement followed the use of 1000 c. c. of 5 per cent. glucose intravenously but soon the lungs became edematous, breathing laboured and pulse poor. Patient expired 38 hours after admission.

Autopsy showed a fibrosed pancreas, cardiac hypertrophy, hypostatic congestion of the lungs, enlarged liver and multiple pyemic absesses of both kidneys with hemorrhage into the calyces and nephrosis. Glycogen present in liver and heart muscles.

The following table (Table IX) summarizes the results of insulin therapy in this case. Because of a slight loss of urine through incontinence the quantity is not exact but this is not very marked, and can hardly be a factor in the reduction of the ketones in the blood, owing to the condition of the kidneys. As the acetone on the breath was faint and soon disappeared, it seems improbable that much acetone was lost via the lungs. The ketones in the blood fell from 80 mg. per cent. to zero in 15 hours, and the CO_2 combining power of the plasma rose from 33 vols. per cent. to 57 vols. per cent. in five hours. From a chemical standpoint the diabetic coma was relieved, but this, of course, would have no influence on the condition of the kidneys. It is interesting to note that, while the ferric chloride reaction in the urine was only faint, nevertheless the Rothera nitroprusside test on the blood plasma was most intense. This is possibly to be attributed to the inability of the damaged kidney to excrete the acid substances. This factor may also have played a part in producing the high initial blood sugar level.

TABLE IX

Date—Time	Urine						Blood					Insulin		Remarks
	Vol. c.c.	Sp. G.	Sug. Gm.	SNP	$FeCl_3$	Ketones Mg.	Time	Sug. %	CO_2 Comb. Power	Ketones Mg. per 100 cc.	Plasm SNP	Time	Units	
3/2/23							12.30 p.m.	.510	33	79.5	4	12.30 p.m.	120	2340 cc. 5% glucose + insulin intravenously.
3.00 p.m.	700		23.5	2	1		3.00 p.m.	.530	48	45.2	1			
							4.00 p.m.	.534	48	24.6	1	4.00 p.m.	20	
							5.00 p.m.	.520	57.1	23.4	1			Fluids containing glucose.
							6.00 p.m.	.546	55.1	6.85	?	6.00 p.m.	20	
							7.30 p.m.	.468	47	.....	?			
							8.30 p.m.	.457	54	17.3	tr.	8.00 p.m.	20	
							9.40 p.m.	.375	55	.....	?			
							11.00 p.m.	.336	31.3	8.8	?	11.00 p.m.	20	1000 cc. 5% glucose intravenously.
4/2/23												1.00 a.m.	20	
3.00 a.m.	60		2.8	1	0		3.00 a.m.	.487	41	0	0	3.00 a.m.	20	600 cc. grape juice and orange juice during night.
							6.00 a.m.	.463	37	3.4	?	5.00 a.m.	20	
												7.00 a.m.	20	
												9.00 a.m.	20	
							11.00 a.m.	.426	52	.....	.....	11.00 a.m.	20	
												1.00 p.m.	20	
							3.00 p.m.	.264	50	.....	.....			3.00 p.m. 1000 cc. 5% glucose intravenously.
							10.00 p.m.	.140	52	.....	0			
5/2/23							2.00 a.m.	.181	46.7	.....	?			
3.00 a.m.	Patient died.													

The carbohydrate equivalent of the insulin administered during the first 24 hours is at least 500 gm. The carbohydrate intake was 165 gm. of glucose given intravenously, plus a small amount of glucose and fruit juices taken by mouth. As the blood sugar falls, it seems certain that all this glucose was metabolized or stored as glycogen. Probably storage would only take place if the requirement for energy had been met and the combustion of fat reduced to a minimum; and we may consider it probable that no more ketones were being produced during this period, as sufficient energy would be obtained without calling on the fats. If the ketone bodies are present in the tissues in the same concentration as in the blood, the amount stored in the body would amount to about 56 gm. and this entirely disappears during treatment. As, according to Wilder[6] and Shaffer[5], ketones are burned in the ratio of two molecules to one of glucose, it seems fair to consider that the combustion of 45 gm. of sugar would account for the burning of these ketones. 30 units of the insulin used should have been sufficient to permit a complete pancreatic diabetic to burn this amount of glucose. The rest of the insulin administered, which under ordinary circumstances would produce a fatal hypoglycaemia, is unaccounted for.

M. L., aet. 26; admitted in coma; died in seven hours.

Three years ago patient was discovered to have diabetes during pregnancy. Diet was used to make the patient aglycosuric, and following parturition she was in hospital for dietetic treatment. She was discharged having a good tolerance but soon dropped the dietetic regime. Her hunger, thirst, and polyuria, according to the husband, have become progressively worse. The day before admission she developed headache, general malaise and general pains with rise in temperature and influenza was diagnosed. Next morning at 7 o'clock she seemed and stated that she was quite well, but was not allowed up. Her husband returned at 2 p. m. to find her in a semi-comatose condition, able to be roused and to take nourishment offered her. At 4 p. m. she did not recognize her sister and was definitely more comatose. Admitted to hospital at 5.40 p.m.

Examination: Well nourished, young woman; temperature 94° F. per rectum; high color; no cyanosis; no edema; breathing irregularly; minute ventilation volume poor; comatose; does not respond to stimulation.

Circulation: Peripheral vessels dilated; heart normal in size; sounds good quality; no murmurs; rate rapid.

Nervous system. Eyes react to light; other reflexes not obtained; anesthetic to pain stimulation.

Respiratory system: Rapid, irregular respirations. No cyanosis. Chest expansion irregular; markedly decreased over lower lobes. Percussion note shows loss of audibility over the right lower lobe at the base

posteriorly; the whole lower lobe is outlined by a distinct decrease in audibility. The breath sounds over the right lower lobe posteriorly have a distinct tubular quality. A few fine crepitations and occasional moist rales are heard. Other areas of the chest normal.

G.U. system: Kidneys not palpable. Urine contains albumin and occasional casts which were not present at the time of the previous admission to hospital.

Diagnosis: Influenza, influenzal pneumonia, diabetes, diabetic coma, nephrosis.

Treatment: The patient was placed in a warm bed with hot water bottles and given 75 units of insulin subcutaneously, followed in one hour by 75 units intravenously. A stomach tube was introduced and 100 gm. of glucose given in 600 c.c. water. The blood pressure was falling at this time and the heart becoming irregular. An additional 50 gm. of glucose was given with 1.0 c. c. of conc. tincture digitalis. At 10:30 the pulse was more irregular, volume poor and B.P. could not be obtained. 1000 c.c. of 10 per cent. glucose were injected intravenously with 500 c.c. of normal saline with temporary improvement, but the patient died in 1½ hours, quite suddenly. Autopsy showed influenzal pneumonia, fibrosed pancreas and nephrosis. The following table shows the results of the analyses in this case. (Cf. Table X.)

Sufficient insulin was given to account for the burning of 225 gm. of glucose or 900 calories—more than sufficient to supply the basal requirement for the period. As the rising blood sugars show, all the sugar given was neither metabolized nor stored in the liver. The ketone bodies in the blood decreased to one-half the original value but the patient showed no improvement. The CO_2 combining power of the blood remained at a very low level throughout. This remarkable fact is paralleled in lesser degree in one of the cases of acidosis reported above. In this case it may possibly be explained as due to a drainage of base into the area of consolidation of the lung. Though this patient, admitted in dying condition with a temperature of 94, undoubtedly died of circulatory failure, it seemed advisable to use large doses of insulin intravenously with sufficient glucose to counteract the tendency to hypoglycemia and the persistent low CO_2 combining power in the plasma furnishes a reason for the administration of small doses of alkali in such cases. Alkali has been given in only one of our coma cases; in this case before the patient arrived in hospital. The coma was not deep and the patient responded to subcutaneous injections of insulin very rapidly. In future, it is felt that small amounts of alkali added to the intravenous injection of insulin and glucose and other symptomatic measures as

TABLE X

Time	Urine						Blood				Alv. CO_2	Insulin		Remarks
	Vol. c. c.	Sp. G.	Sug. Gm.	Ketones			Time	Sug. %	Ketones Mg. per 100 c.c.	CO_2 Comb. Power		Time	Units	
				SNP	$FeCl_3$	Mg								
6.00	1250	1032	24.3	3	2	3420	5.45	.591	91	9	15	6.15	75 subcut.	B.P. 86/60; Tem. 94°F. per rectum.
							7.45	.736	71	9	14	7.30	75 intravenously	6.50–100 gm. glucose by stomach tube. 7.45–B.P. 76/50. 8.00–50 gm. glucose 350 c.c. water by mouth. 9.45–B.P. unobtainable. 11.00–1000 c.c. 10% glucose intravenously plus 500 c.c. saline.
							9.45	.660	66	9.5				
								1.00	47	9				
12.00	83		2.6	2	1	127								

required will give more satisfactory results than insulin and glucose alone.

G.A., aet. 47; weight 87 lb.; best weight 125 lb.; admitted October 11, 1922, 6.30 p.m.; died October 13, 1922, 10 p.m.

Thirty-two months previous to admission patient was well, then noticed the onset of great thirst, failing eyesight, loss of weight and strength, and polyuria. One year ago sugar was found in the urine and she was given a diet in which the only foods prohibited were those made with sugar and wheat flour. Her condition apparently did not change until October 2, 1922, when she suffered an injury to the right ankle. On evening of October 10 was well except for some pain in the right ankle; was observed to be drowsy next morning and was difficult to rouse at 1 p.m., but refused to come to hospital. B.P. 120/68. Acetone odor on breath. Became comatose. Admitted to hospital at 6.30 p.m., 11/10/22.

Previous illnesses: Frequent "bilious" attacks.

Family history: Mother had diabetes.

Examination. A pale, emaciated woman; skin dry, scaly; marked dehydration. Tongue dry and glazed. Strong odor of acetone on breath. Cannot be roused; makes no response to painful stimuli; makes no movements; relaxed atonic muscles. Reflexes absent. Breathing shallow, long drawn out and irregular. Accessory muscles of respiration active.

Respiratory system: Some moist rales in both bases posteriorly.

Circulatory system: Pulse rate slow; volume poor. Pressure low. Moderate thickening of vessels. Heart shows no enlargement to right or left; sounds weak; systolic apical murmur. B.P. 80/60.

Digestive system: Liver and spleen not palpable.

Nervous system: Completely comatose; no reflexes obtainable.

Treatment: The patient was given digitalis and atropine per hypo immediately, and later camphor and caffeine. At 6.45 p.m. insulin 120 units, and 1000 c.c. of 10 per cent. glucose solution were given slowly intravenously to avoid overtaxing the heart. 40 units of insulin were given subcutaneously at 8 p.m. At 8.30 p.m. the patient showed the first sign of improvement by starting to phonate. B.P. at this time 80/60. At 9 p.m. she moved about in response to painful stimuli. At 9.30 the patient opened her eyes and looked about the room and answered questions. Said she was thirsty and drank water through a straw. Biceps jerks present at this time and eyes were noted to react to light. Her family were brought in and she recognized and talked with them. She was given caffeine sodium bensoate gr. iii, q 3 h per hypo, and 700 c.c. of normal saline. 40 units of insulin were given at 10.45 p.m. and repeated at 12 midnight, 4 a.m. and 8 a.m. Fluids containing glucose and fruit juices were given freely by mouth from 10 p.m. The blood pressure at 12 midnight was 78/50 but gradually fell through the night. The patient slept some but made intelligent responses when roused. At 10 a.m. her blood pressure was 40/20. Pituitary extract, ½ c.c. every hour, was given per hypo, and 750 c.c. of 10 per cent. glucose containing 100 units of insulin were given intravenously. 40 units of insulin were given subcutaneously q2h from 1 p.m. till midnight and thereafter as in the accompanying table. During the day the patient remained conscious but drowsy

and weak. She knew her friends and talked with them and responded to directions. The pulse rate remained the same, 116-120, only slowing to 70 about 2 hours before death. The heart sounds were weak. There was no cardiac dilatation. The body and extremities were quite warm but slightly cyanosed. The blood pressure readings were as follows: 11.10 a.m. 40/20; 12.30 p.m. 40/15; 2 p.m. 38/20; 5 p.m. 31/20; and from then on the blood pressure could not be recorded. The second morning the patient refused fluids and it was difficult to get her to take anything by mouth thereafter. During the day the temperature gradually fell to 95° F., associated with an increase in the cyanosis. The patient recognized relatives in the afternoon but gradually became more difficult to rouse and for the last two hours could not be roused. Respirations ceased at 10.30 p.m., 52 hours after admission. An autopsy, performed shortly after death, showed a small hard pancreas, 60 gm. in weight, and the presence of a nephrosis. Glycogen was present in the liver, heart and psoas muscle. The accompanying table (Table XI) shows the chemical results.

The clinical picture presented by this patient is different from any case of diabetic coma I have previously observed and most resembles those cases of carbon monoxide poisoning, who recover partially to a weak but conscious condition only to die in the course of a few days. It is remarkable for the peculiar condition of weakness and consciousness persisting two days with recognition of people, responses to questions, perception of orders and muscle response to them but absolute lack of volitional effort of any kind. This was associated with a long period of very low blood pressure during which practically no urine was secreted and which did not respond to stimulation. The heart action was weak but it seems apparent that peripheral vasodilatation was partly responsible for the blood pressure level. A somewhat similar "toxic" condition is sometimes seen in patients slowly dying from new growths. In these patients, as in our present case, there is an agonal retention of non-protein nitrogen in the blood stream. It is suggested that, in this case, there occurred a permanent damage to the nervous system with loss of vasomotor control and of the higher mental functions, which ultimately caused the death of the patient.

The patient excreted practically no acetone in the urine after the first eight hours following admission. Though the CO_2 combining power of the plasma rose to double its original value, 12.8-25 vols. per cent., the latter figure represents severe acidosis. The blood ketones, however, rapidly fell to zero. In her lethargic state the energy requirements could be supplied from the glucose and fruit juices given. The high blood sugar levels and the presence of glycogen in the liver and muscle post mortem show that

TABLE XI

Date—Time	Urine						Blood				Insulin		Remarks
	Vol. c.c.	Sp. G.	Sug. Gm.	Ketones SNP	Ketones $FeCl_3$	Ketones Mg.	Time	Sug. %	CO_2 Comb. Power	Ketones Mg. per 100 c.c.	Time	Units	
11/10/22 6.30—10 p.m.	840	1020	24	4	3	4854	6.40 p.m.	5.35	12.8	123	7.00 p.m.	120	6.30 p.m. admitted unconscious. B. P. 80/60 Insulin plus 100 gm. glucose intravenously.
							9.00 p.m	5.45	12.8	121	8.00 p.m.	40	Subcutaneously. 8.30 Phonation. B. P. 80/60.
											10.45 p.m.	40	9.00 Moves when pinched. 9.30 Speaking, drinking.
12/10/22 10 p.m.—2 a.m.	530	1020	13.8	2	2	1275	12.00 m.	5.87	17.6	79	12.00 m.	40	12.00 B.P. 78/50.
							3.00 a.m.	5.87	14.7	60	4.00 a.m.	40	Conscious, drowsy.
											8.00 a.m.	40	10.00 B.P. 40/20.
2—6 a.m.	50	1019	1.4	1	1	160	6.00 a.m.	5.78	23.3	44	10.00 a.m.	100	Plus 75 gm. glucose intravenously.
											1.00 p.m.	40	B.P. 40/20; cyanosis.
											3.00 p.m.	40	B.P. 38/20.
6 a.m.—4 p.m.	75	1016	1.1	1	1	22	4.00 p.m.		19.5	20	5.00 p.m.	40	B.P. 31/20.
											8.00 p.m.	40	
											10.00 p.m.	40	B.P. does not record.
											12.00 p.m.	40	Cyanosis.
4 p. m. 12th to 10.45 p.m. 13/10/22	75	1012	.273	0	0	0	2.00 p.m.	5.43	25	0	4.00 a.m.	40	Refuses nourishment.
											8.00 a.m.	40	
											10.15 a.m.	40	Recognizes friends.
											1.00 p.m.	40	Movements weak. Cyanosis.
											3.00 p.m.	40	
							10.45 p.m.	1.56	25	0			Heart blood immediately post mortem—N.P.N. 96 mg. per 100 c.c.

plenty of carbohydrate was available for use. 860 units of insulin, equivalent to at least 860 gm. of carbohydrate, and perhaps much more, were used in this case without the development of hypoglycemic symptoms, though far in excess of the available carbohydrate or energy requirement of the patient. This suggests a use for insulin apart altogether from its function in the utilization of carbohydrate and gives rise to the interesting speculation whether the ketone bodies are not burned under the influence of insulin.

Discussion

Two cases are reported as typical of the successful results obtained in the treatment of diabetic coma by insulin. One illustrates the use of subcutaneous injection of insulin, and the other the employment of insulin intravenously in order to obtain more rapid effects. It is considered advisable to use carbohydrate in addition to insulin in order to prevent hypoglycemia and to reduce the combustion of fats to a minimum. The results of treatment in each case were satisfactory from a clinical point of view. The tables given illustrate the severity of the condition and the satisfactory outcome of treatment from the chemical point of view. Large amounts of acetone bodies in the urine are reduced to negligible values. Similarly the large quantities of ketones in the blood disappear and the CO_2 combining power of the blood becomes normal again. Such cases justify the conclusion that insulin is a specific in the treatment of diabetic coma.

Three fatal cases of coma are reported because of the additional light thrown on the treatment of this condition. Two of them present complications,—one, influenzal pneumonia; the other, pyemic abscesses of the kidney—both sufficiently severe to cause a fatal outcome. In both these cases, despite the severe complications, the administration of insulin had a definite effect on the ketones. The third case, G.A., presents a syndrome so far as known not previously seen in diabetes, which may represent an end stage of ketone poisoning.

In the case reports, attention has been drawn to the extraordinary tolerance to insulin in coma. Apparently the ordinary carbohydrate equivalent value of the insulin, as found in other patients, bears no relation to the requirement during severe acidosis and coma. Nor, if rough calculations be even approximately correct, does the amount of energy produced or carbohydrate burned bear a relation to the insulin utilization, even

regarding the patient as an absolute diabetic requiring artificial insulin for the combustion of protein and glycerol. There is the possibility that much larger quantities of insulin are required to store carbohydrate as glycogen over that required in the combustion of carbohydrate, but we have no evidence on this point. Since, in these cases, we have provided sufficient carbohydrate and insulin to supply all the calories necessary, the combustion of additional fat from the body must be at a minimum. The amount of ketone bodies in the blood and tissues of some of these cases could not have been less than 50 gm. As this completely disappears during insulin treatment and cannot be accounted for by excretion in the urine and expired air, we must consider that much the larger part of it is burned or synthesized into some nontoxic body, possibly carbohydrate in nature. If the latter were the case we might have an explanation of those rare cases of diabetes in which, under careful control, the D:N ratio appears to be decidedly more than 3.65:1. The former alternative appears at the present time to be the more probable one. The significant facts are that the ketone bodies themselves are disposed of in the presence of large amounts of insulin and one may not unnaturally hazard a guess that these two facts are related to each other in a more than casual manner.

Insulin will not, of course, exert any influence on associated diseases from which the patient may die though relieved of the condition of acidosis. Further, it appears probable that, in prolonged severe coma, a toxic effect is produced on the nervous system similar to the nephrosis produced in the kidney by the ketone bodies, from which the patient does not recover. If this is true the sooner the insulin is administered the better will be the result, and in this way intravenous injection is superior to subcutaneous injection. In early coma, as in severe acidosis, it is probable that subcutaneous injection of the insulin will suffice and certainly it is much the easier method.

The clinical symptoms of coma may not correspond in their severity with the condition of the patient, and one may find too late that resort to intravenous medication is necessary. The subcutaneous administration of insulin immediately on diagnosis of a very severe acidosis or incipient diabetic coma will no doubt be of value in checking the progress of the condition. Further treatment, it is felt, should be carried out in hospital where greater facilities are available than in a private home. The clin-

ical points on which this requirement for insulin should be based are: acetone odor on the breath; prolonged or irregular breathing; general evidence of dehydration—dry skin, loss of tissue turgor, nausea, emaciation and, particularly, a dry, glazed tongue. A patient with a tongue moist at the edges is relatively safe for several hours at least.

Large quantities of carbohydrate are useful in the treatment of coma with insulin for three reasons: (1) it prevents hypoglycemia when large doses of insulin are used; (2) it furnishes energy and reduces to a minimum the incomplete combustion of fat and protein, and thus limits ketone production; (3) it aids in the combustion of ketones already present in the blood and tissues. In the severe cases glucose may be given intravenously. The possible theoretical damage the administration of excess carbohydrate might do to the pancreas of a diabetic in coma should not be weighed against the reasons for its administration. It may be pointed out that the pancreas in this condition is apparently producing no insulin and the patient must depend on that artificially supplied. The measure is a temporary one only and should not be continued beyond the period necessary to get the patient back on a suitable diet with or without insulin. Fluids are valuable in the treatment as a vehicle for carbohydrate, for promoting diuresis and for relieving dehydration. Water, broths and various fruit juices may be used.

The value of alkalies in the treatment of diabetic acidosis and coma has been debated for many years, and opinion still seems to be rather evenly divided on their usefulness. All agree that excess of sodium bicarbonate in these cases does harm to the patient and this is responsible for the firm stand a number of clinicians have taken against its use. Certain evidence reported above may throw some light on this condition and help to explain the divergence of opinion. There is a very general tendency, even in fatal cases of coma, for the CO_2 combining power of the plasma to rise to the lower limit of normal when the ketones in the blood are removed by insulin administration. In two of the fatal cases (G.A. and M.L.) the alkali reserve remained at a very low level in spite of the reduction in blood acetone bodies. One case (R.K.), recorded under acidosis, demonstrates the necessity for and use of alkali treatment in this condition. In this patient the administration of insulin diminished the ketone bodies in the blood from 62 mg. per cent. to normal values, abolished the

ketonuria and raised the alveolar CO_2. With this occurred clinical improvement in the patient's condition, and a rise in the CO_2 combining power of the plasma from 24 vols. per cent. to 38 vols. per cent., at which level it remained constant for 12 hours. The administration of mineral salts, including alkali, raised the CO_2 combining power of the plasma from 38 vols. per cent. to 56 vols. per cent. with much clinical benefit to the patient. The base deficiency in the coma cases referred to above was not due to volatile acids and they may be compared to other types of acidosis, such as in severe nephritis, uremia, etc., in which the use of moderate amounts of alkali is known to be of value in increasing the comfort of the patient, decreasing the dyspnea, etc. It is suggested on these grounds that the judicious use of alkali may prove of value in some cases of diabetic coma. As a therapeutic measure alkali, if necessary at all, should be given as early as possible and, since the absorption of substances introduced into the stomach during coma is most erratic, the administration should be by the vein. Unfortunately, since the decision must rest on a constantly low CO_2 combining power with a rapidly diminishing amount of acetone bodies in the blood, there is at present no practical means of differentiating those cases requiring alkali from those who do not, and necessarily the alkali must be given to all cases. At the same time the harmful effect of an overdose to patients not really requiring alkali must be guarded against. Palmer and Van Slyke[4] showed that, in normals, the reaction of the urine altered to that of blood when the CO_2 combining power of the plasma was raised to 71-75 vols. per cent., and that one gm. of sodium bicarbonate would raise the CO_2 combining power one vol. per cent. in a person weighing 84 lb.* Since the CO_2 combining power of the plasma in most cases rises to about 50 vols. per cent. one might introduce in all cases 20 gm. of sodium bicarbonate per 84 lb. body weight with safety. This might be of material benefit in the type of case reported. Further amounts of alkali might be introduced later if chemical evidence of its necessity is obtained.

* In pathological cases particularly, where, as in diabetic coma, there is damage to the kidney, the reaction of the urine does not furnish a reliable indicator for alkali requirement.

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THE BLOOD SUGAR FOLLOWING INSULIN ADMINISTRATION AND THE SYMPTOM COMPLEX—HYPOGLYCEMIA

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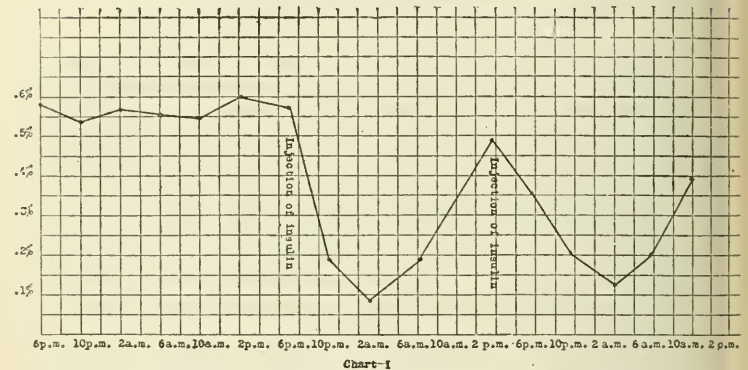
The effect of insulin on the blood sugar of diabetic dogs was observed by Banting and Best[1] in their original investigation. Subsequently the effect of insulin on the blood sugar of normal rabbits was studied by Banting, Best, Collip, Macleod and Noble[2]. These observers found that, with the fall in blood sugar, the rabbit exhibits characteristic symptoms, the earliest of which are hunger, thirst, hyperexcitability and apparent fear. It was further found that, when the blood sugar falls to about .045 per cent., convulsions occur which could be controlled by the subcutaneous injection of glucose. They suggested that the occurrences of these convulsions be used as a basis for the physiological assay of insulin.

In March, 1922, a preliminary clinical report was made showing the blood sugar lowering effect of insulin in diabetes mellitus[3]. In January, 1923, a further report was made in which the clinical symptom complex—hypoglycemia—and its treatment was described[4].

In human beings, after the administration of insulin, two separate and distinct phenomena have been observed: first, an increased utilization of carbohydrate in diabetics; and secondly, in both diabetics and normals, a lowering of the blood sugar level. Our clinical experience would indicate that, in the treatment of severe cases of diabetes mellitus, units of insulin drawn from the same batch of extract have a fairly constant carbohydrate utilization value. When this value has been determined in one patient, a similar increase in the carbohydrate utilization may be anticipated in other patients following the administration of the same dose. The blood sugar lowering effect of insulin, on the other

hand, is by no means so constant. Since the blood sugar lowering effect of insulin in animals is the basis of the present method for physiological assay, and in man, as in animals, is associated with a very definite symptom complex, the variation in the blood sugar lowering action of insulin is of practical interest.

When a single dose of insulin is given there occurs a fall in the blood sugar percentage which reaches a low point, sometimes as early as two hours, sometimes as late as twelve after the administration, and tends to return to the original level at a variable rate. (See Chart I.) As a rule glycosuria ceases as the blood sugar per-



Chart—I

centage falls from .2 to .17 and reappears as the blood sugar rises above this level. But cases have been observed in which this threshold was as high as .3 per cent. and as low as .1 per cent.

To determine the variations of this blood sugar lowering effect in different patients, a batch of insulin of known potency was set aside. Its physiological assay was 10 units per c.c., while clinical assay indicated that 1 c.c. would account for the utilization of 15 grams of carbohydrate. Various patients, diabetic and non-diabetic, were selected and to each 20 units of insulin was given at 8 a. m., followed by a breakfast of non-nutrients. Previous to this no food had been given for 14 hours. The blood sugar was taken immediately before the injection of the extract and at intervals, generally of one hour, for four hours. In two cases these hourly blood sugar estimations were carried on for two or three

hours longer when it was expected that the low point would be delayed. In these two cases, a lunch of non-nutrients was given at noon. Five of the patients were not diabetics; four of these were suffering from chronic arthritis and one convalescent from bronchitis. Previous to the experiment they had been given the ordinary ward diet. The remaining fifteen were diabetics. Some of these were given their injection during their regular course of insulin treatment. In one or two insulin treatment was just being started. With three exceptions, they had, for several days previously, received maintenance diets according to the calculation described in an earlier article. (Blood sugar determinations are given in Table I.) Patient 12, with the fasting blood sugar of .163 per cent., was receiving a diet 50 per cent. above the maintenance level. The 16th patient, with fasting blood sugar .208 per cent., had received an extra 200 grams of bread the previous day. Patient 20, with the fasting blood sugar of .356 per cent., was receiving a diet in which all constituents had been increased 100 per cent. There is also included in the table a column of (a) the lowest blood sugar obtained in each case, (b) the initial blood sugar minus the lowest blood sugar—the absolute fall, (c) this absolute fall in per cent. of the initial blood sugar. The results are given graphically in Chart II. In a few of the curves it is probable that the lowest point has not been reached but our experience has been that, with the lower initial blood sugars at any rate, the low point most frequently occurs before the four hour estimation, and even with the higher initial blood sugar the low point is not much delayed.

The number of estimations of this blood sugar lowering effect does not furnish sufficient data from which to draw final conclusions. From the results obtained, however, certain points may be observed. In the first place there is not any very evident difference between the effect observed in non diabetics and the effect observed in diabetics. It might be pointed out further that all the diabetics were severe cases and, where the initial blood sugar level was low, this level had been obtained by previous insulin treatment. On the other hand, there does appear to be a tendency for the fall to be dependent on the initial blood sugar level. When the results are tabulated in order, according to the initial blood sugar, the blood sugar fall tends to increase with the higher initial blood sugar.

There is no very constant relationship in the percentage value

TABLE I

Showing the fall in blood sugar following the administration of 20 units of insulin in diabetic and non-diabetic patients

Case No.	8 a.m.	9 a.m.	10 a.m.	11 a.m.	12 Noon	1 p.m.	2 p.m.	3 p.m.	Lowest Blood Sugar	Initial Blood Sugar Minus Lowest B.S.	Blood Sugar Fall in Per Cent of Initial B.S.
1*	.089	.090	.083	.120	.080	....	....	....	080	009	10.1
2*	.094	.079	.070	064	075	....	....	....	.064	.030	31.9
3*	.10	.083	.068	.064	063	....	....	....	.063	037	37.0
4*	.113	.071	.091	.077	.107	....	....	....	.071	.042	37.1
5	.118	....	....	071	.071	....	....	....	071	.037	31.3
6*	.12	.093	.096	.088	.099	....	....	....	088	.032	26.6
7	.133	.099	.089	.077	.082	....	....	....	.077	.056	42.1
8	.148	.133	.125	.102	.100	....	....	....	100	.048	31.0
9	.154	.163	.153	.089	.088	....	....	....	088	.066	42.8
10	.160	.147	.133	.107	.077	....	....	....	077	.083	51.8
11	.161	.172	.137	.090	.068	....	....	....	068	.093	57.7
12	.163	.143	.122	.094	.090	....	....	....	.090	.073	44.7
13	.182	.174	.141	.10	.10	....	....	....	.10	.082	45
14	.20	.192	.182	.120	097	....	....	....	.097	.103	51.5
15	.20	.178	.138	.097	086	....	....	....	.086	.114	57
16	.208	.186	.175	.128	.110	....	....	....	.110	.098	47.8
17	.208	....	....	.182	.160	....	....	....	.160	.048	23
18	.280	....	....	.21	.170	....	....	....	.170	.110	39.2
19	.330	....	....	.182	.158	.174	.154	....	.154	.176	53.3
20	.356	....	....	.270	.217	.199	.20	.207	.199	.157	44

*Non-diabetic patient.

of the low point in terms of the initial blood sugar. In the graphs many of the curves approach each other as the blood sugar falls. This is due to the fact that, whereas the first sixteen blood sugars

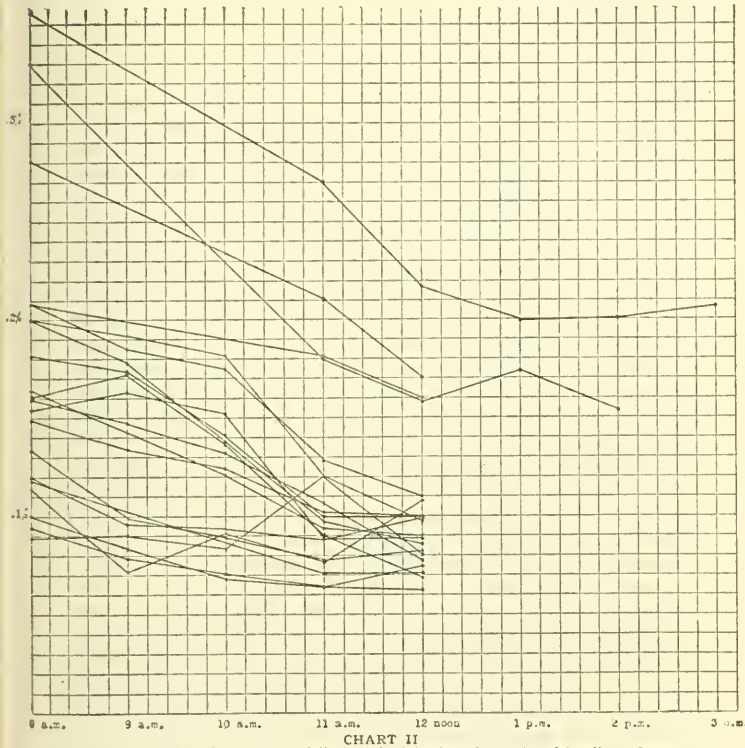


CHART II

Showing the fall of blood sugar following the injection of 20 units of insulin at 8 a.m.

lie between .089 per cent. and .208 per cent., the low point lies between .063 per cent. and .110 per cent. It is conceivable that, in these sixteen cases, the blood sugar level is readily reduced to normal with this dose of insulin but that larger doses would be

required to lower the blood sugar level below normal. In the last four cases, with higher blood sugars, it is possible that the dose is inadequate to lower the blood sugar even to normal levels.

In Table II figures are given of the blood sugar estimations in two patients, following different doses of the same batch of insulin as that used above. The same technique was followed throughout. The first blood sugar figure is the fasting level at 8 a. m. The insulin was injected immediately after the 8 a. m. blood sugar determination, followed by a breakfast of non nutrients. In case H the fall in blood sugar bears a direct relationship to the size of the dose but the relationship is not an arithmetic one. 10 units brought about a fall of .057 per cent; 20 units a fall of .082 per cent; and 30 units a fall of .10 per cent. At a later date 20 units of insulin was given to this patient when the fasting blood sugar was .118 per cent. and the fall then was only .047 per cent., again showing the dependence of the fall upon the initial blood sugar level. In case D five injections were made, 10 units, 20 units, 30 units twice and 50 units. Here the results are not quite so regular. 10 units produced a fall of .037 per cent, 20 units .083 per cent., 30 units .081 per cent, and at a later date 30 units produced a fall of .118 per cent. from a somewhat higher initial blood sugar. 50 units produced a fall of .088 per cent. from a somewhat lower initial blood sugar. The first patient was on a constant diet throughout the time these estimations were made. The second patient was on a constant diet during the 1st, 2nd and 3rd estimations and an increased diet during the 4th and 5th. These two series of results show that the degree of fall does not bear any accurate relationship to the amount of insulin given. In the second patient, 20 units brought about a greater fall than 30 units, and almost as great as 50 units. The results are given graphically in Charts III and IV. There is no mathematical relationship between the fall and the amount of insulin given so that, even under carefully controlled conditions, estimation of the blood sugar lowering effect of insulin in diabetic patients does not appear to be of much value for the purpose of determining the relative potency of various preparations of the extract. In these determinations all the low points lie between .071 per cent and .113 per cent. with one exception, although the maximum dose was five times the minimum dose. It appears again that in the diabetic the blood sugar level is easily reduced to the normal range by insulin but somewhat less easily reduced below this.

TABLE II

Showing the fall in blood sugar following the administration of varying amounts of insulin in patients H and D

Case	Amount of Insulin	8 a.m.	9 a.m.	10 a.m.	11 a.m.	12 Noon	1 p.m.	2 p.m.	3 p.m.	Lowest Blood Sugar	Initial B. S. Minus Lowest B. S.
H.....	10 units	.170	.196	.166	.137	113	....	....	....	.113	.057
	20 units	182	.174	.141	.110	.10	....	....	....	10	.082
	30 units	.185	.152	.085	.091	....	....	....	....	085	.100
	Later 20 units	.118	....	....	071	.071	....	....	....	.071	.047
D.....	10 units	.172	.189	.147	.138	.135	....	....	....	.135	.037
	20 units	.160	147	133	.107	.077	....	....	....	.077	083
	30 units	.182	.164	.178	.120	.101	....	....	....	.101	081
	30 units	.20	142	.132	.106	.082	....	....	....	.082	.118
	50 units	.152	....	....	.077	.074	.068	.072	064	064	088

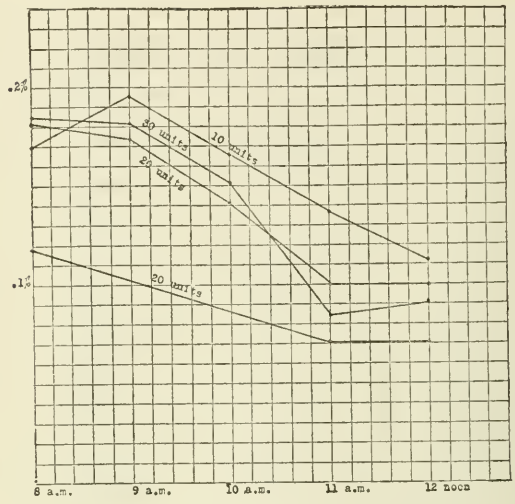


CHART III

Showing the fall in blood sugar following the administration of varying amounts of insulin in patient "B"

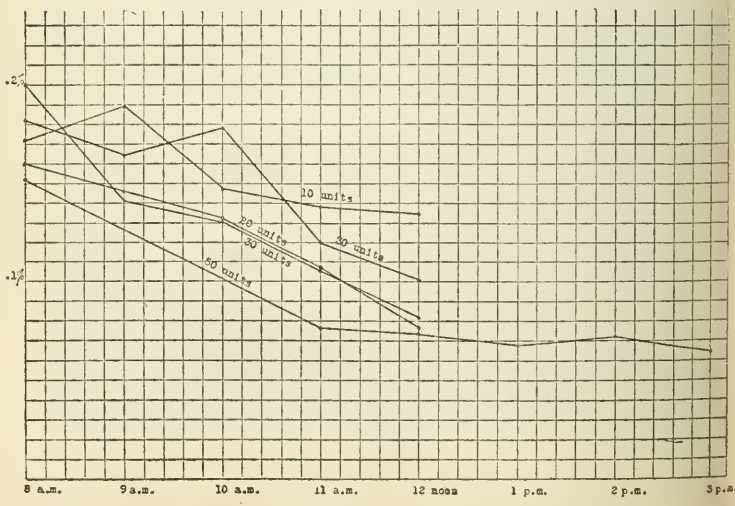


CHART IV.

Showing the fall in blood sugar following the administration of varying amounts of insulin in patient "D"

The Clinical Symptom Complex—Hypoglycemia

There is then, in most patients, a considerable range in the amount of insulin which will result in a fall of the blood sugar to the normal fasting level. When a dose in excess of this amount is given a further fall in the blood sugar level occurs and, at the same time, there results a group of symptoms which is quite characteristic. A relationship between the lowered blood sugar level and the occurrence of these clinical phenomena appears to be so well established that we refer to them as hypoglycemic reactions.

The initial symptom may be a feeling of nervousness or tremulousness, sometimes a feeling of excessive hunger, at other times a feeling of weakness or a sense of goneness. The level at which a patient becomes aware of the fall in blood sugar is fairly constant for that individual, although this is not always the case. When a reaction has already been experienced the onset of a subsequent one is usually recognized by the patient when the blood sugar percentage falls to some point between .08 per cent. and .07 per cent. The reaction may go no further than this of its own accord or it may be cut short at this stage by the administration of carbohydrate. More usually it is rapidly followed by objective signs—most frequently a sweat which may be very profuse; pallor and flushing is common; sometimes a change in pulse rate. In children this increased pulse rate is often the means of detecting hypoglycemia; in adults the sweat is the outstanding feature. At the same time the subjective symptoms become more severe; the feeling of nervousness may become definite anxiety, excitement, or even emotional upset. The feeling of tremulousness is possibly a form of incoördination. Patients have shown a loss of power to perform fine movements with their fingers. Actual tremor has not been observed at this stage. At times there is a feeling of heat or cold, sometimes of faintness. Some have complained of vertigo; others of diplopia. This is the extent of most reactions, and the blood sugar is usually between .07 per cent. and .05 per cent. Much more severe manifestations are observed with further lowering of the blood sugar. Marked excitement, emotional instability, sensory and motor aphasia, dysarthria, delirium, disorientation, confusion, have all been seen. Syncope or collapse may occur, rarely going on to a state of unconsciousness. The blood pressure has fallen in one or two cases, but more often it is well sustained. Bradycardia has occurred. One case, while un-

conscious, showed absence of muscle jerks; another, loss of sphincter control. Increased muscle tonus and tremor may occur during recovery from the unconscious state. Convulsions have not been seen.

Many blood sugar estimations have now been made at the time of these reactions and, in general, the severity of the reaction depends upon the blood sugar level. Occasional variation, however, has been observed both as to the blood sugar level at which a reaction begins and the level at which it becomes severe. There are patients who become aware of the hypoglycemia when the blood sugar is between .08 per cent. and .09 per cent. On the other hand, other patients have experienced no symptoms at levels as low as .054 per cent. A severe reaction has been observed with a blood sugar percentage of .060 per cent., and a determination of .04 per cent has been obtained during the course of a mild reaction. A blood sugar percentage of .035 per cent. is usually accompanied by unconsciousness. The lowest blood sugar observed was .025 per cent. This was in a patient with influenzal broncho-pneumonia during a severe reaction which occurred at night. Administration of glucose brought the patient out of hypoglycemia.

It is still premature to speculate as to the meaning of these hypoglycemic phenomena. It is noteworthy that the symptoms are largely associated with the nervous system. It is also evident that the blood sugar level alone does not entirely account for the disturbance, for blood sugar determinations are often obtained between .06 per cent. and .08 per cent. under normal conditions. The phenomena must be more complex. It is possibly associated with the physicochemical properties of the sugar remaining in the blood stream after insulin has been administered.

Certain factors may be considered in the production of clinical hypoglycemia. When the blood sugar is low at the time of the injection there is a greater liability to reaction than when the blood sugar is high. It is often observed that a patient under treatment will have a lower fasting blood sugar each successive morning before the day on which the reaction occurs. But, independent of the initial blood sugar, some patients go into reaction more easily than others. In those patients who are extremely undernourished, reactions have been generally more severe and more prolonged. Reactions should be anticipated when insulin is first given, and, on account of the uncertainty of the potency under present methods of assay, they have also been met

with more frequently when a new preparation of insulin is administered. The danger of hypoglycemia is intimately associated with the whole problem of the timing and division of insulin dosage. Even when the insulin given has been accurately balanced against the carbohydrate of the food, reactions are sometimes met with due, no doubt, to some unusual delay in the absorption of food. There is an especial element of danger in the possibility of hypoglycemia at night. The occurrence of a reaction is usually two hours after insulin administrtion but its onset is sometimes delayed and patients have been found in reaction at 1 a.m. subsequent to a 5 p.m. injection. Probably during the evening the food absorbed from the evening meal offsets the influence of the insulin and, when the assimilation of the food is complete, there remains sufficient insulin to bring about a reaction.

The Treatment of Hypoglycemia

In hypoglycemia a number of substances have been tried to control the symptoms and restore the blood sugar to normal. The sensation of hunger is sometimes intense and patients may be satisfied by anything to swallow. The most satisfactory results are obtained with glucose but quite good results are obtained with other sugars. Orange juice has been used successfully in controlling the symptoms, probably because of its content of glucose and levulose. It seemed possible that glycerol would prove an effective means of control on account of the fact that it behaves in other ways similar to a carbohydrate. This proved to be true but results are not so rapid as when glucose itself is given. Epinephrin, 1/1000 sol., 1 cc., furnishes a ready means of controlling hypoglycemia when the patient is unconscious. In the most severe cases it is better to give epinephrin and then give glucose intravenously as well, as there may be delayed absorption from the alimentary tract. Less severe cases may be given glucose as soon as they can swallow. The rapidity with which recovery takes place in these cases is extraordinary and is directly dependent upon the rise in the level of the patient's blood sugar. Patients have received other substances, such as hot coffee or tea and beef extracts, and soon declare that they are feeling quite well again. However, there is no persistent increase in the blood sugar level and the patient again complains of the severer symptoms of hypoglycemia.

The following protocols show the blood sugar levels in two cases of hypoglycemia treated at first by hot coffee and beef extract respectively, and showing disappearance and reappearance of symptoms and their relief by means of glucose ingestion. Occasionally these substances suffice to clear up all symptoms and the patient never has physical signs (sweating, etc.) of the condition. The mechanism of this we do not know, but surmise that it is associated with an increased blood flow through the liver and digestive organs washing out a small amount of glucose.

CASE I.

9.30	Premonitory symptoms of hypoglycemia.
9.45	Blood sugar .061 per cent. Hot coffee given, with apparently complete relief.
10.10	Blood sugar .055 per cent.
11.00	Patient perspiring and complains of subjective sensations of hypoglycemia. 25 grams glucose given.
11.10	Patient relieved of subjective sensations and suffered no further inconvenience.
12.30	Blood sugar .139 per cent.
1.20	Blood sugar .134 per cent.

CASE II.

10.20	Patient complains of subjective sensations of hypoglycemia for past half hour.
10.30	Blood sugar .067 per cent. Hot beef extract given, with relief of sensations temporarily.
11.45	Symptoms have gradually returned; patient now perspiring freely. Blood sugar .055 per cent. 20 grams of glucose given.
12.05	Patient relieved of symptoms. Blood sugar .109 per cent.

The response to small doses of glucose is prompt and lasting as a rule. Often 5 grams of carbohydrate will tide a patient along until the next meal. We often give 20 grams and, if the reaction occur in the evening, a dose of glucose based on the carbohydrate equivalent of the last insulin injection is given to obviate the possibility of a later reaction during the night. Rarely, when high dosage of insulin is being used, a second reaction may occur due to insufficient carbohydrate being used in the first instance. It may be controlled in the same manner as the first.

Sooner or later it is likely that all patients will experience hypoglycemic reaction. The most likely occasion is when patients are changing from one batch to another. The comparatively small size of batches still makes this change quite frequent and one has a choice of an elaborate mixing of batches and observation of the blood sugar levels, or using a half dose and permitting

glycosuria and gradually working up to an adequate dose—in the process not seldom encountering reaction—or else of going boldly ahead and risking hypoglycemia. When the carbohydrate equivalent of the dose needed is small it is probable that the last is the best procedure. In this case the reaction, if the batches of insulin are nearly equal, may not occur for several days and can be foretold and forestalled by observation of falling blood sugar levels before it occurs. The blood sugar level is not known to many patients who have been discharged from hospitals and we find it advisable that each patient should experience a reaction before leaving the hospital. Such a patient is quick to recognise the onset of a second reaction, as the early symptoms in a given case are very characteristic. The remedy is easily obtained and administered, and we advise patients to have near them the requisite carbohydrate at all times, either in the form of oranges, glucose candies, corn syrup, or cane sugar. Subsequent doses of insulin should, of course, be lower in the number of units. Reaction may also occur after a patient has been on a certain batch of insulin for a time, due to an increase in the patient's tolerance for carbohydrates. The blood sugar in this instance tends to fall slowly and is an indication that food must be increased or the dosage of insulin decreased. If neither of these is done the reaction may occur repeatedly at the same time but with increasing severity each successive day. With the average severe diabetic hypoglycemia has not presented a serious problem, but special nursing precautions may well be taken if insulin is administered late in the day, to guard against the possibility of a fatal reaction occuring during sleep.

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INSULIN IN HOSPITAL AND HOME.

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Introduction: During each successive month since August 7, 1922, when the insulin treatment of diabetic patients was begun in this clinic in Boston, confidence in it has increased and our original expectations have been more than fulfilled. The clinical benefits reported in the publications from Toronto[1, 2] have been fully confirmed. To our severest cases, selected with deliberation from those treated during the last 24 years, it has given additional food, weight, and strength of body and mind.

Insulin* is not a cure for diabetes, but it is a potent preparation, alike for evil and for good. Thomas D. omitted insulin for 5 days, continued his diet, developed a mild infection, and entered the hospital to die seven and one-half hours later of coma. A patient with a tolerance for 114 grams carbohydrate took one unit and the blood sugar fell to 0.03 per cent. Conversely Miss M., our first case and the severest diabetic on our list, who had gone down to the street from her apartment but once in 9 months, felt able after 6 weeks of treatment to walk with ease 4 miles daily, has gained 10.5 pounds, and now cares for her invalid mother. Mrs. M. with rapidly ascending gangrene, fever, 5 per cent. sugar, and marked acidosis, was first seen Sunday evening, brought to the hospital, given insulin, and the thigh amputated at 10 the next morning by R. C. Cochrane. After 8 days the 30 unit daily dose of insulin was omitted; 10 days later she became sugar-free and remains so today while upon an adequate diet. With similar temporary help of insulin, Mrs. D. successfully withstood two carbuncles, the second requiring an incision 10 inches long. Aune N., three years of age, was on the verge of coma, came out with insulin, and was discharged taking carbo-

* All the insulin (iletin, Lilly) used in the treatment of the patients and in the investigations here recorded was furnished through the courtesy of the Eli Lilly Co. upon the recommendation of the University of Toronto. To their manifold and unvarying helpfulness and kindness during all these months, expressed through Dr. G. H. A. Clowes, Dr. A. L. Walters, and Mr. Irvin Paige, we extend our cordial thanks.

hydrate 76 grams, protein 37 grams, fat 46 grams, calories 59 per kilogram body weight. Aune remained sugar-free eventually with 3 units of insulin in the morning and the same dose or at times none at night.

Insulin is a remedy which is primarily for the wise and not for the foolish, be they patients or doctors. Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more brains. Two ignorant patients, who were helped by insulin and needed it, went home without wishing to take it, and their physicians, though living nearby, did not take the trouble to come to the hospital either to see the patients or learn about insulin. An alert little girl of 15 after six weeks of dietetic treatment and a little insulin was not sugar-free on 36 calories per kilogram, yet she was wise and with insulin has gained 21 pounds, 25 per cent. of her body weight. Her elderly, over-worked country doctor traveled 150 miles to see for himself this new form of treatment and continued it at home!

For two years Mary G., nine years of age, has adhered to her rigid regime, fasting one day weekly and never eating over 732 calories in 24 hours. She remains a shadow, but like Pershing before Lafayette's tomb, she is "here," and now her mother has the satisfaction of watching her eat a saucer of oatmeal at breakfast. She knows how to take her own insulin. Mrs. B. has learned, through love and innumerable Benedict tests, that Billy B. needs but one injection of insulin every third afternoon, provided he has one injection each morning. Thus with 4 units every third day and 2 units the others his calories have been increased 34 per cent. and his weight 3 pounds from the lowest level.

The number of diabetics who have been admitted to institutions under our care since insulin was received August 7, 1922, is 204, of whom 83, or 40 per cent., have been treated with insulin. Save for the boy who died 7½ hours after he entered there has been no death from coma in the hospital during this period. Furthermore, there has been no other death from coma among the cases treated with insulin after they have been discharged to their homes. The statistics upon which this paper is based end January 25, 1923.

Small doses, usually under 30 units a day, have appealed to us, feeling better satisfied to see many patients gain a little than a few patients much. Even now with insulin more plentiful we

prefer very moderate doses. Overnutrition is harmful in health, doubly harmful in diabetes, and we see no reason why insulin should make it safe. We do not believe in diabetic patients walking on insulin stilts any more than is necessary.

Insulin has revolutionized diabetic treatment in more ways than one. First it can give more food, strength, and weight, but secondly to do this it demands not only a knowledge and respect for the diabetic diet on the part of the doctor and patient, but adherence to the same, if the diabetic wishes to get his money's worth for the insulin he injects.

For the wise, who may be rich or poor, young or old, and for the innocent, who can be cared for, insulin is a benefit, but for the ignorant, who likewise may be rich or poor and young or old, it can be dangerous, and a gift of free insulin to such is like casting away pearls.

Selection of Patients

Early in August a list of about 30 of the severest cases of diabetes was made, chosen from those surviving diabetics treated since 1898. To this number another group of about 30 severe cases has been added from time to time, including several cases representing surgical emergencies. Recently some twenty-five other cases who were of distinctly less severe type, yet either quite unable to maintain weight upon a diet which they would tolerate or notable because of some peculiarity, have been selected. To all of these patients insulin has been given. Of the total number of 83 cases treated, seven are (to use Woodyatt's term) "pedigreed" diabetics in that they have already found their way into medical literature. These are Cases No. 632, 866, 1305, 1542, 1794, 2174, 2560. These pedigrees deserve a scientific dignity far surpassing the current emphasis on the "family history," especially in view of the attention increasingly given nowadays to "after-histories." Multitudes of case reports in the literature are totally useless, for want of a follow-up.

Number of Units of Insulin Used

Most of the patients have begun with 1 unit of insulin one, two, or three times daily, and this has been increased almost daily until the requisite number of calories could be taken to allow a gain of weight and of strength. It has been our policy to treat many rather than few diabetics. We have felt it more humanitarian to

prolong the lives of many old and faithful patients rather than to attempt to secure marvelous results with a few. Up to now such improvement might have been at the sacrifice of the life of another. The problem presented to us was to keep 60 cases, in more or less desperate straits, alive. Marvelous results can be foreseen from the moderate results in Table 1, and will in reality be reported we hope from other clinics less pressed by accumulated old patients.

There are four cases of the fifty-three treated who still are taking less than 5 units a day. These patients have been much helped by insulin. They have gained an average of 4 pounds in a total of 53 days or one pound in 13 days. In contrast are 12 cases who are known now to be taking 20 units or more, and these patients have gained an average total of 6 pounds in a total of 90 days. The largest number of units given a patient regularly is 60, and this patient, Case No. 2256, has gained but 5 pounds in 147 days. Her strength however has increased markedly, and there is comparatively little doubt but that weight will come, too. This patient developed diabetes in February, 1919, and when she came for treatment in June, 1921, her weight had fallen to 72 pounds. Mental depression has been a factor of serious significance in this case. This began originally in 1921. She recovered from it when the urine became sugar-free, but in 1922, when improvement was slow with insulin, it returned. She has simply existed since the summer of 1921 until insulin has begun to give her a new lease of life. To some extent this patient's mental condition can be attributed to false hopes aroused by newspapers which are not published in this vicinity, for our friendly editors, we are glad to say, have co-operated in refraining from the temptation to get news at the expense of extravagant hopes aroused in patients. She is now receiving 54 calories per kilogram body weight. Her weight still remains 48 per cent. below standard.

Summary of Protocols of Fifty-three Cases Treated with Insulin

The total number of cases treated with insulin since August 7, 1922, has been 83, and 53 of these are available for statistical purposes. The remainder have either had insulin transitorily in emergencies of some kind, later to be described, have been followed too short a period to merit discussion (i. e., less than 15 days), or because of lack of insulin have been treated with

obviously such small dosage as to make inclusion in this table unfair. The five deaths which occurred in the entire group are discussed in another place, though it may be said here that in no instance, save that already mentioned of Thomas D., was insulin related to the death of the patient.

In Table 1 are recorded the age at onset of the diabetes and at the beginning of treatment, the number of days during which insulin has been administered, the total number of units of insulin given, and the analyses of sugar in the urine and blood at the beginning of treatment and at the last observation. The data upon the weight are recorded in detail.

Duration of Treatment and Number of Units Administered

Miss M., Case No. 1542, is the longest under treatment, having been observed for 165 days, though upon 7 days no insulin was administered subcutaneously. During this period she has received 2,555 units. This number of units is exceeded only by Case No. 2801. Though the latter, a girl of 15 years with adolescent goitre, began treatment a little later, she has received 3,246 units and is one of the patients receiving over 30 units daily. Case No. 2256 comes next in number of units taken, and is destined to surpass the other two, because in a shorter period she has been given 2,464 units.

The table also furnishes information to some extent on the number of units taken in successive months. Fourteen cases have been treated for 30 days or less, and these cases have averaged 11 units per day. Sixteen cases have been treated between 31 and 60 days, and these cases have averaged 12 units per day. Thirteen cases have been treated between 61 and 90 days, and have averaged 11 units per day. Seven cases have been treated between 121 and 150 days, and have averaged 11 units per day. Finally, three cases have been treated for 151 or more days, and have averaged 11 units per day. At the present writing there are eleven patients who are not taking over 10 units, thirty-seven patients who are taking between 11 and 20 units, and two patients who are taking between 21 and 30 units, and three patients who are taking 31 or more units. Encouragement, therefore, is justifiable in the belief that from month to month the dosage of insulin need not be increased.

TABLE I

Summary of Protocols of Fifty-Three Patients After Treatment With Insulin

Case No.	Age		Treatment		Analyses				Weight									Calories Per Kg.	
					Fasting Blood Sugar		Urinary Sugar		Preceding Treatment			During Treatment							
									Computed Dressed in Lbs.			Computed Naked in Kilograms							
	At Onset	Beginning of Treatment	Duration Days	Insulin Total Units	Beginning	Latest	Beginning	Latest	Maximum	Relation to Standard At: Maximum	Relation to Standard At: Beginning of Treatment	Beginning	Latest	Lowest	Loss in First Two Weeks	Gain From Lowest Level		Prior to Treatment	Latest Report
	yrs.	yrs.			%	%	%	%	lbs.	%	%	kgs.	kgs.	kgs.	kgs.	kgs.	%	cals.	cals.
632	30	40	47	338	0.16	0.13	0	0	185	+16	−30	49.2	51.1	48.9	0.3	2.2	4	23.6	35.0
866	31	39	69	664	0.23	0.22	0.1	0	165	−13	−50	42.5	43.5	42.0	0.5	1.5	3	26.1	37.3
1469	10	15	31	324	0.14	0.13	0.1	0	...[1]	....	−32	38.6	40.8	37.9	0.7	2.9	7	28.8	35.8
1500	41	49	134	796	0.11	0.16	0	0	145	− 5	−32	46.0	46.4	42.8	2.3	3.6	8	22.4	28.1
1542[2]	37	42	158	2555	0.33	0.22	1.6	occ.[3]	157	+10	−44	34.7	36.1	33.2	0.6	2.9	8	27.6	33.8
1544	48	55	34	164	0.21	0.17	0.3	1.5	213	+21	−15	64.5	62.8	61.5	0.5	1.3	2	19.5	25.5
1616	5	8	75	1011	0.17	0.18	1.8	0	...	....	....	13.0	15.1	12.7	0.2	2.4	16	47.3	59.8
1750	36	42	74	915	0.26	0.24	0.2	occ.	155	+18	−34	40.3	42.3	40.3	0	2.0	5	22.8	30.9
1889	13	17	64	860	0.16	0.20	0	0	...	....	−37	28.6	31.4	28.6	0	2.8	9	36.6	49.6
1895	14	16	66	592	0.25	0.25	0	0	...	....	−26	43.6	45.7	43.6	0	2.1	5	23.0	37.0
1931	42	48	21	220	0.29	0.21	0.3	0	186	+21	−28	46.8	46.5	45.5	1.4	1.0	2	24.2	31.2
1970	42	51	61	448	0.26	0.18	0.3	0	182	+36	−16	51.1	54.5	51.0	0	3.5	6	12.3	26.1
1997	11	14	26	402	0.30	0.18	0.6	0	...	....	....	36.6	40.0	35.0	0.5	5.0	13	26.9	31.2
2024[4]	11	13	50	586	0.27	0.26	1.5	0.8	...	....	....	(1)24.4 (2)25.6	28.4 27.3	24.4 25.0	0 0.6	4.0 2.3	14 8	33.3	37.9
2063	14	18	66	646	0.26	0.19	0	0	...	....	−28	33.3	36.1	31.9	1.4	4.2	12	32.3	42.1
2174	44	45	67	554	0.29	0.27	1.3	0.2	188	+29	−32	43.2	44.5	42.3	1.2	2.2	5	33.1	34.1
2256	14	18	147	2464	0.24	0.26	0	0.3	...	....	−47	26.5	26.1	23.9	0	2.2	8	35.8	53.6
2271	13	14	31	374	0.22	0.14	3.3	0.3	...	....	....	33.9	36.1	33.6	0.3	2.5	7	20.4	31.9
2290[5]	55	59	14	85	0.26	...	0.9	0.1	160	− 2	−34	44.5	46.8	44.5	0	2.3	5	22.8	32.9
2296	30	39	15	209	0.18	...	4.2	0.1	140	− 3	−20	50.0	49.5	49.5	0.9	0	0	18.6	32.4
2304	47	50	133	1275	45	0.14	0.3	0	175	+26	−34	39.2	45.7	38.3	1.0	7.4	16	20.9	26.5
					0.32	0.22													

2366	14	16	30	493	0.30	0.16	1 2	0	...	....	−32	31 6	30.5	29.3	2.2	1.2	4	29.2	42.4
2397	42	43	136	1291	0.32	0.14	0.6	0	125	−10	−36	38 6	39.1	37.5	1.1	1.6	4	28.8	30 8
2419	15	17	34	465	0.16	0 13	0.6	0	..	....	−32	38 3	39.2	38 2	0 1	1.0	2	32.0	42.3
2422	35	39	57	688	0.23	0.14	0	0	146	+ 3	−47	34 2	37.4	34.1	0 1	3.3	9	27.1	35.4
2448	17	18	39	428	0.24	0.29	6.5	1.2	123	−10	−20	46.4	51 7	46.4	0	5.3	10	18.7	28.9
2508	4	5	63	530	....	....	0	occ.	...	....	....	12 3	14.1	12 3	0	1.8	13	42.2	67.8
2551	26	33	54	814	0.24	0.13	0.4	0	140	+ 5	−27	40.9	42.3	40.8	0.1	1.5	4	14.8	39.6
2560	5	7	48	142	....	....	0	0	...	....	....	18.2	19.1	17.7	0 2	1.4	7	44.3	56.2
2626[6]	61	68	16	169	0.26	0.25	0.8	0.5	279	+52	+ 2	81.0	79.8	79 3	1 6	0.5	1	24.7	26.7
2662	12	13	36	356	0.15	0 08	0	0	...	....	....	27.5	30.9	26 8	0.2	4.1	13	20.2	35.2
2668	12	17	85	1215	0.24	0.11	0	occ.	...	....	....	26 3	29.8	26.1	0.2	3.7	12	24.4	54.5
2687	23	25	53	2411	0.45	0 26	2.5	0	122	− 9	−34	37.7	42.4	37.7	0	4 7	11	15.0	32.5
2702	28	31	154	1572	0.26	....	0.3	0 4	144	+16	−37	34 9	40.5	31.5	0.6	5.5	14	26.4	23.1
2725	16	20	158	880	0.24	0 16	0.2	0.9	126	−10	−29	42.3	44.1	42.3	0	1.8	4	26.5	32.2
2729	21	22	73	1196	0.22	0 19	0.2	occ.	168	+ 4	−28	48.8	51.1	46 5	2.2	4.6	9	24.2	29.7
2746	5	7	144	572	....	....	0.4	0 3	...	....	....	13.0	15.9	12.7	0	3.2	20	43.0	48.1
2776	8	10	16	177	0.25	....	0.3	0	...	....	....	24.0	25 5	23 8	0.2	1.7	7	20.1	38.0
2783	36	38	42	420	0.22	0.22	0.2	occ.	155	+10	−21	50.9	52.0	50.8	0.1	1.2	2	25.9	30.0
2784	15	17	21	336	0.31	0.13	0.4	0	117	− 7	−27	38.6	38.2	38.1	0.5	0.1	0	12 5	30.3
2801	15	15	149	3246	0.19	0.36	1.2	0.3	117	+12	− 3	46.7	40.7	37.4	2.2	3.3	8	15.5	18.2
2802	14	15	142	1132	0.24	0.27	0	occ.	...	....	−27	32.5	39.5	29.8	0	9.7	25	19.9	27.3
2876	58	62	77	628	0.20	0.20	0.1	occ.	175	+22	−26	45.5	43.6	43.1	1.8	0.5	1	17.0	31.6
2877	6	7	58	167	....	0.10	0	0	...	....	....	19.3	20.2	19.1	0.2	1 1	5	32.4	56.0
2919	3	4	70	759	....	....	1 0	0	...	....	....	13.6	15.4	13.6	0	1.8	12	30.1	62.1
2943	31	35	41	608	0 30	0.19	1 2	0	150	−10	−24	54.5	55.4	53.6	0	1.8	3	11.4	30.1
2948	27	28	24	302	0.25	0 23	0.3	0	142	+ 4	−18	48.6	49.0	48.6	0	0.4	1	26.6	30.7
2962	12	12	14	89	0.20	0.08	0.6	0.3	...	....	....	41.1	41.3	40.7	0.4	0.6	2	16.9	41.4
2970	23	25	16	73	0 21	0 19	0 1	0	172	+27	−25	44.7	48.2	44 7	0	3.5	7	21.8	25.6
2972	65	67	54	524	0 28	0 19	1 5	0	149	+ 8	−45	31.6	35.9	31.4	0.2	4 5	13	19.2	35 1
2975	6	9	22	186	....	....	0 2	0	...	....	....	20.8	21.4	20.8	0	0 6	3	37.7	50.1
2978	1	2	16	143	....	....	0 7	1 1	...	....	....	8.6	8.2	7.7	0 9	0 5	6	55.3	85 0
2979	3	3	28	269	....	....	2.3	0	...	....	....	13.9	15.0	13.6	0.3	1.4	9	14.5	57 7
Total 53	aver	ages	63	712	0 21	0.19	0.8	0.2	...	....	−29	36.4	38 0	35.5	0 5	2 6	7.5	26.0	38 2

[1]All cases under 15 years of age at time of maximum weight and at beginning of treatment excluded from column of standards.

[2]Case No. 1542 actually under treatment 165 days. Insulin omitted, seven days. Maximum weight reached during treatment, 83½ pounds on January 5. Owing to infection weight fell to 78 pounds on January 18.

[3]Occ.=Patient reports from home "sugar occasionally present." Not included in average.

[4]Case No. 2024 had two periods of treatment, Sept. 25-Oct. 13 and Dec. 14-31, with no insulin between the periods.

[5]Case Nos. 2290, 2296, 2776, 2962 have data calculated to include January 25. All other data includes January 18.

[6]Case No. 2626 reports sugar-free on January 31 for the first time in 9 years.

The Blood Sugar at the Beginning and in the Course of Treatment

It was our expectation that the fasting blood sugar would be much higher at the latest observation than at the beginning of treatment, first because of the increase in total glucose in the diet, and second because the last blood sugar test was made so long, as a rule 14 hours or more, after the last dose of insulin that its effect would have disappeared. On the contrary *the latest average percentage of blood sugar is 0.19 per cent., while the first was 0.24 per cent.* Whether a series of data compiled a few months later with these same patients would present such favorable results, time alone can answer.

Urinary Sugar

Comparatively few cases began insulin when the percentage of sugar in the urine was high. Response to dietetic treatment is so rapid that patients were made sugar-free, or nearly sugar-free, as a rule in the first few days in order to save insulin. A considerable number did not yield to dietetic treatment, yet during the week preceding the commencement of insulin, fasting was employed on but 9 days with 8 patients. With the 53 cases, described in Table 1, during the present observations fasting was not employed. The average percentage of sugar in the 24-hour quantity of urine at the beginning of treatment with insulin was 0.8 per cent. and at the latest observation was 0.2 per cent. As 48 of these patients are now undergoing treatment in their own homes, this percentage of sugar is perhaps greater than would be the case if they were still in the hospital.

Weight

The maximum weights of adult patients are easy to secure, but with children are obtained with far more difficulty. In Table 1, therefore, we have been obliged to omit data which we should have been glad to include regarding patients under 15 years of age. For the other patients the rule holds that overweight preceded diabetes. In 19 instances of the 29 cases in which the maximum weight is known, it was above standard. It was not as much above standard as one often sees, but this is not strange, because the patients were younger than the majority of diabetic

patients, and furthermore, were of a severer type, and that type is usually not to be found in the obese.

Evidence of the severity of the disease and of the havoc which it has wrought upon these patients is shown by the percentage below standard weight at the beginning of treatment. In one instance this reached 50 per cent. and in 13 instances it was 30 per cent. or more.

During the first two weeks of treatment with insulin the weight frequently decreased, and the average decrease for the 53 patients amounted to 0.5 kilogram. The lowest weight during this period was taken as the basal weight of the individual and the gain in weight subsequently was computed therefrom. Loss of edema and the low diet, prescribed in order to banish glycosuria, account in large measure for this loss in weight in the first two weeks. It is true that sometimes a gain in weight also results in the first two weeks, because of the marked desiccation of patients at entrance. In one instance this amounted to 9 pounds, but this case does not appear in the table as he came for treatment within the last 12 days.

The actual gain in weight for the different patients has varied from 9.7 kilograms in Case No. 2802 to no gain in weight in Case No. 2296 who has been but 15 days under observation. The average gain in weight for all the patients has been 2.6 kilograms, or 5.7 pounds per patient.

The percentage gain in body weight is a better guide to the improvement in the patient following insulin than is the absolute gain in weight. With some of the cases this has been considerable. It happens that the greatest actual gain in weight coincides with the greatest percentage gain in weight; thus, Alice S., Case No. 2802, has gained 25 per cent. and now weighs more than ever before in her life. On the other hand, Case No. 2746, a little boy of 5 years, has gained but 3.2 kilograms, but this amounts to an increase of 20 per cent. for his tiny frame. The average percentage gain in weight for the 53 cases is 7.5 per cent.

The average calories per kilogram body weight taken by the patients prior to the beginning of treatment was 26 calories, and the average calories which the patients were taking according to their latest reports was 38 calories. In one instance, possibly two, the gain in weight has gone ahead so rapidly that the patient now is actually receiving less calories per kilogram body weight than at the beginning of treatment. These patients will serve

very well as tests to show whether gain in weight is bringing any recuperative power to the pancreas. From the series of cases here recorded it is too early to express any opinion in this regard.

The gain in calories has been in calories of carbohydrate, protein, and fat. When one considers that a patient can live for years upon 15 grams of carbohydrate, but that to do this the diet must be restricted to 5 per cent. vegetables, a little cream and occasionally a few strawberries or grape fruit, the change in range in diet which insulin has brought is evident. The average number of grams of carbohydrate which these 53 patients were taking at the beginning of treatment was 37, but at the latest report was 45, which is an increase of 22 per cent. The greatest increase in carbohydrate recorded for any patient was 132 grams, or 80 per cent., and the least increase was 1 gram. The actual gain in carbohydrate utilized averaged more than 8 grams, because more of the carbohydrate was lost in the urine at the beginning of treatment. From what follows it will also be seen that the total glucose (Woodyatt) utilized very greatly increased. With protein, too, considerable increases were made, but as a rule, especially in young children, the protein was not allowed to go over 3 grams per kilogram body weight. So many of our patients were upon a very low protein diet at the beginning of treatment that this component of the diet was raised proportionately more than carbohydrate. The patients were very glad to have an increase of only 20 per cent. in carbohydrate if their protein could be increased 50 per cent. The average number of grams of protein was 36, or 1 gram per kilogram body weight, at the beginning of treatment, and at the end was 55 grams, or 1.4 grams per kilogram. The greatest increase in calories was in the form of fat. At the commencement of treatment the average number of grams of fat was 62, and at the end was 105 grams. It will be noted that for an average gain of 8 grams of carbohydrate, there was an average increase of 41 grams of fat; in other words, a ratio of 1 gram of carbohydrate to 5 grams of fat. If one estimates the ketogenic antiketogenic ratio in the first diet it will be found to be 1.1 and in the second 1.2, each a ratio which is well below the limits of acidosis.

Age of Patients at Beginning of Treatment with Insulin

Our experience with insulin shows that it can exert its full power from babyhood to old age.

Case No. 2979, 3 years old, came out of threatening coma with diet and insulin with unusual readiness, and Mrs. H., Case No. 2972, 68 years of age with 524 units of insulin used in 54 days, gained from 69.5 pounds to 79 pounds. At both extremes of life unusual conditions may prevent such favorable results; thus, Olive O., Case No. 2815, who developed diabetes in September, 1922, at the age of 2 years, 10 months, but was kept sugar-free only intermittently until entrance to hospital on January 5, 1923, was not rendered sugar-free with 238 units of insulin. At present she has developed an acute respiratory infection and though the diet is carbohydrate 36 grams, protein 40 grams, fat 58 grams, she does not keep sugar-free with 16 units daily. The little girl has been much disturbed with the injections and the nervous element may be a part. The present infection is a most unfortunate complication. Likewise, at the other end of life, Mr. S., Case No. 2626, who developed diabetes at the age of 61 years, came for treatment with a septic foot on May 2, 1922, but eventually recovered under the surgical care of Dr. R. C. Cochrane. He began insulin January 3, 1923, and at present has 20 units daily. With the addition of 12 grams of carbohydrate to his diet, the quantity of sugar in the urine has not increased, but it did not decrease, (though today, January 31, we learn that the glycosuria which had been 0.2 per cent. has disappeared for the first time in nine years). This recently favorable course leads us to be cautious before being doubtful of the good effect of insulin on this patient or at his age. A somewhat similar case is that of Mrs. M., Case No. 2980, whose leg was amputated for gangrene. Insulin appeared to help in the emergency, but the 30 units daily were omitted 8 days after the operation and during the 10 days following she gradually became sugar-free without it and has been able to increase her carbohydrate since. Still another patient, Mrs. L., Case No. 2908, seen in consultation was found to be taking 30 units of insulin daily. With this patient the insulin did not appear to have any advantageous effect because the sugar in the urine did not markedly increase when the insulin was omitted. The glycosuria yielded to diet though she did not become actually sugar-free until the carbohydrate was reduced to 35 grams.

Insulin, therefore, can act favorably with both extremes of life, but does not necessarily act favorably, and whether heroic doses will bring about favorable results must be left in abeyance so far as this clinic is able to report.

The age of the cases treated with insulin is recorded by decades in Table 2. Since many of these cases have been under observation for a short period or have been treated simply for emergencies in a temporary fashion the number of cases available for statistics is reduced. The table shows both the gain in weight and gain in per cent. body weight per patient and the average number of days required to secure with these patients a gain of one pound. It will be observed that the gross gains in weight are quite evenly distributed between the different decades, but that

the percentage gains are highest in the younger patients. There is no particular difference in the number of days which the old and young have required to gain a pound of weight.

Diabetes in the first decade of life is considered to reach the acme of severity.

TABLE II

Age of Patients at Beginning of Treatment with Insulin

Age by Decades	Total No. of Cases	Cases Available for Statistics	Av. Gain in Weight per Patient		Average No. Days for Gain of 1 Lb.
			Lbs.	Per Cent	
0—10	14	10	4	10	13
11—20	19	18	7	8	10
21—30	9	4	8	7	7
31—40	13	7	5	5	13
41—50	11	8	6	7	15
51—60	8	3	5	4	7
61—70	7	3	4	5	12
71—80	2	0	..	..	..

Age of youngest, 2 years.
Age of oldest, 77 years.

The youngest patient with diabetes, longest under our personal observation, who has been given insulin is Frederic G., Case No. 1616, who first came for treatment September 1, 1919, showing 3.8 per cent. of sugar and ++ acidosis. Between that period and his return to the hospital on November 3, 1922, he was free from glycosuria for about 6 months, but during 1922 on account of taking food it has been impossible to keep him sugar-free, and the glycosuria has varied between 1.4 per cent. and 4.4 per cent. The little boy was so hungry that he would burn his hands taking food out of a hot oven, would get up at night when others were asleep to secure food. On November 3, 1922, his parents brought him back to the hospital saying, "Dr. Joslin, do anything you want with Frederic, you can't make him any worse." At that time he was carried in on a cushion, but about two weeks after his return home his mother reported that he was carrying a gun on his shoulder while marching with the other children and on January 26th again writes, "He is feeling fine and would not touch a particle of food other than his diet. He walks down town every afternoon and it is amusing to see the children on the street look at him because he has not walked any for the last two years." Nothing we can say based upon laboratory results can equal in importance statements of this character.

Frederic G. had more reactions from insulin than any other patient, but Frederic G. had derived from insulin unusually good results. Between November 4, 1922, and January 18, 1923, he has taken approximately 1011 units of insulin and has gained 4.75 pounds or 17 per cent. body weight.

Dorothy Z., Case No. 2508, lives 114 miles from Boston, developed diabetes July 7, 1921, has been under our observation since January 31,

1922, and has lost 13.75 pounds from her highest weight. She returned for treatment with insulin on November 16, 1922. Since that time she has taken about 530 units and gained 4.25 pounds. The greater part of the gain in weight and the greater part of the gain in strength took place in her home. During the first two weeks of treatment with insulin at the hospital she could not walk upstairs but now "walks up and down stairs, and dances with her brothers."

Billy B., Case No. 2560, developed diabetes on June 15, 1921, and did not begin any treatment whatsoever until March 1, 1922. He about held his own with dietetic treatment until December 2, 1922, when he commenced to take insulin. Since that period he has remained 18 days in the hospital, but in his home, 118 miles from Boston, he has continued the treatment, gained 2.25 pounds, takes 2 units of insulin each morning and every other day 2 units in the afternoon.

Betsy A., Case No. 2746, developed diabetes on November 10, 1920, was treated with unusual care in Texas by her physician, came for treatment on August 2, 1922, was started with insulin on September 2, 1922. Experience in treatment was so meagre that her dosage was small, which accounts for her comparatively slight gain. She went home after 4 weeks of insulin treatment in the hospital, has continued it under her physician's care and now, after an interval of 5 months, records a gain of 6.5 pounds, 22 per cent. of her original body weight. She was one of the severest cases of diabetes to come under our care.

The effect of insulin injected into the nose and its effect when inhaled from a cotton plug moistened with insulin and inserted into the nostrils was tested with this child. For the purpose a special preparation of insulin (iletin, Lilly) was furnished me by the Eli Lilly Company. Dr. Herman kindly cooperated in the tests. To the negative results obtained not much importance can be attached because of our inexperience with the method and our one month's experience with insulin.

Rita W., Case No. 2877, developed diabetes at the age of 7 years, entered the Corey Hill Hospital on October 25, 1922, with severe acidosis, distinctly on the borderline of coma, and with 4.0 per cent. of sugar. With a total of 37 units of insulin in 21 days and rearrangement of the diet glycosuria disappeared and she was discharged after remaining in the hospital 5 weeks upon a diet containing carbohydrate 49 grams, protein 39 grams, fat 63 grams, 47 calories per kilogram body weight without insulin. Since that date she has at one time or another shown sugar, but reports on January 18 as being sugar-free, satisfied with her diet and now taking 2½ units insulin. The gain in weight is 2 pounds or 5 per cent. She evidently requires more food and probably more insulin.

Jack K., Case No. 2919, is another little boy who developed diabetes at 3 years of age. His brother died of diabetes. He came for treatment on November 9, 1922, weighing 29 pounds, which represented a loss of 7 pounds since the onset of the disease. When he entered the Leatherbee Boarding House he could barely raise his legs up to the two piazza steps. During nearly 3 weeks the glycosuria did not disappear in a 24-hour

specimen. He had 2 reactions from insulin, but at the end of the period played almost like a normal child and his mother writes January 17th that "This winter for the first time in 3 years Jack has been free from otitis media." His history shows a record of having had 13 punctures of the middle ear for this condition. He is now sugar-free and weighs 33.75 pounds, a gain of 16 per cent. *His improvement took place largely in his home.*

Betty C., Case No. 2931, developed diabetes on November 28, 1922, came for treatment on November 29, 1923, with 3.4 per cent. of sugar and +++ + acidosis. In the following 10 days she received in addition to her diet a total of 44 units insulin, when it was then omitted, and 9 days later was discharged without insulin from the Corey Hill Hospital on a diet containing carbohydrate 58 grams and calories 1013, or 63 per kilogram body weight. She has remained sugar-free since and has required no insulin. Her gain in weight since coming for treatment has been but a quarter of one pound. Her case serves as a contrast to cases treated continuously with insulin. So far as dietetic treatment is concerned, she would have been considered in pre-insulin days as having done very well.

Florence J., Case No. 2776, developed diabetes in February, 1921, at the age of 8 years and has been under our dietetic treatment since that time. She re-entered the hospital on January 7, 1923, with 2.4 per cent. of sugar and +++ acidosis. In the subsequent 3 weeks she has received a total of 225 units of insulin. The urine is now sugar-free. The carbohydrate in her diet is 44 grams and the calories 1120. She has gained 4 pounds in weight or 7 per cent.

Lois N., Case No. 2975, is a little girl who has much difficulty in keeping sugar-free at home. She first came under our dietetic treatment in January, 1921, but returned to the hospital for insulin on December 18, 1922. Since then she has received a total of 186 units of insulin during 22 days, has become sugar-free, gained 1.25 pounds or 3 per cent. body weight and her appearance is that of a healthy child.

Mary G., Case No. 1949, developed diabetes in May, 1920, at the age of 6 years, 10 months, and came under our dietetic treatment on October 13, 1920. She has been seen but on four occasions in the last two years. With the help of a nurse for one month in her home she became sugar-free and her mother learned the details of the diet. In the intervening period of two years she has constantly kept sugar-free and fasted one day each week. She returned for treatment on January 20, 1923, and though her diet has been increased rapidly, she remained sugar-free until January 27, 1923, although receiving only one unit of insulin twice daily. Already she needs and is receiving more insulin. The tolerance for the increased diet for the first week is simply due to the two years of under-nutrition. In this respect, she resembles Mr. P., who was 50 per cent. below standard weight and did not show glycosuria until 14 days after his diet was increased without insulin.

SEE TABLE 6.

It is easy to develop too much enthusiasm about the effect of insulin in these children of the first decade. Before one draws conclusions one should bear in mind that of the 47 fatal cases of diabetes in the first decade which we have treated without insulin, the average duration of life was 2.7 years and that 7 of these cases lived 5 or more years.

Duration of Diabetes of Patients Taking Insulin

Insulin acts strikingly both upon recent cases of diabetes and upon cases of long standing. The duration of the disease in the patients who were given insulin is shown in Table 3. This varied from 6 weeks (Olive H., Case No. 2962) to 23 years (Mrs. R., Case 2201). Measured by gain in weight the cases of shortest duration advanced the most if the gain is estimated on the percentage basis, but if in pounds, the results are the same for the cases of short and long duration. If estimated by the number of days required to gain 1 pound in weight, the early cases again had the advantage. The average number of days required for a gain of one pound varied for the different years of duration between 8 and 19 days, being longest in the sixth year and shortest in the first and ninth years, in other words duration was not of account.

TABLE III

Duration of Diabetes of Patients Treated with Insulin

Years	Total No. of Cases	Cases Available for Statistics	Gain in Weight per Patient		Average No. Days for Gain of 1 Lb.
			Lbs.	Per Cent.	
Under 1 year	11	8	7	9	9
1— 2.....	14	12	6	8	10
2— 3.....	11	7	5	7	12
3— 4.....	9	6	8	11	11
4— 5.....	10	7	6	8	11
5— 6.....	7	4	4	5	19
6— 7.....	4	2	3	3	14
7— 8.....	3	2	2	1	13
8— 9.....	3	2	6	6	18
9—10.....	3	1	8	6	8
10—20.....	7	2	5	4	13
20—30.....	1	0	..	..	..

An endeavor was made to determine the effect of insulin upon patients who had developed diabetes most recently.

The case of shortest duration was Olive H., Case No. 2962. With this girl of twelve years diabetes developed December 10, 1922, and she was brought for treatment on January 11, 1923, showing 9 per cent. sugar in

the urine. She was placed upon the routine test diets, became sugar-free in 4 days, with insulin on third and fourth days, and eventually developed a tolerance for 155 grams carbohydrate and 41 calories per kilogram body weight. Cases of short duration often make remarkable gains in tolerance, but seldom, if ever, have the gains in tolerance for carbohydrate and for calories as well been as great. From the chart it will be seen that insulin was used, beginning with 3 units two times a day on the third day of treatment, and continued up to the last day, the doses being increased to 4 units two times a day. Whether the patient will continue to need insulin is a question. It is our intention to omit it later for a few days, note the result, and according to the indication which that teaches, treat the patient. We shall endeavor to maintain the carbohydrate in the diet at the same high level and the calories as well unless the patient gains an undue amount of weight.

TABLE IV

Insulin in Diabetes of Recent Onset

Olive H., Case No. 2962

Date 1923 Jan.	Diacetic Acid	Urinary Sugar	Diet in Grams				Naked Weight (Lbs.)	Blood Sugar	Insulin (Units)
			C	P	F	Cals.			
11	++	9.0	...	..	..	....	..	....	
12–13	+++	5.3	23	13	14	200	90	....	1
									2
13–14	0	0.6	66	24	37	693	90	0.20	2
									3
14–15	0	0	35	15	30	466	89	....	3
									3
18–19	0	0	73	51	70	1126	90	0.08	3
									3
23–24	0	tr.	155	68	88	1684	90	....	3
									3
									3
25–26	0	tr.	155	68	88	1684	90	0.10[1]	3
29–30	0	0.1	155	66	88	1676	90	0.10[2]	4
									4

[1]Fasting. 1 Hour after insulin.

[2]2 Hours after breakfast. 2½ hours after insulin.

Another early case is a little Finnish child of 3 years, Aune N., Case No. 2979, who illustrates well the use of insulin in an early case and the help which insulin can render in acidosis. The symptoms of diabetes began on October 24, 1922, and sugar was discovered on December 3, 1922. The patient entered the hospital with 4.5 per cent. of sugar and +++ acidosis upon December 18, 1922. The diet was gradually changed, but acidosis increased, and the fifth night after admission we found her about midnight with the drowsiness warning of early coma. *Insulin had not been started when she entered the hospital, but insulin was given in 3 doses of 2, 4, and 4 units during the remainder of the night. Thirty-six hours later the child had so far recovered that she sat up in bed, played*

at the window, and threw a kiss at the doctor on his leaving the room. Twelve units of insulin were then being given daily. The diet was steadily increased, and on January 15, 1923, the carbohydrate was 76 grams, protein 37 grams, and fat 46 grams, calories 866. Insulin was omitted occasionally before supper, and in consequence a trace of sugar appeared in the urine, promptly to disappear the next day when insulin was resumed. Since returning home the patient has been reported as being sugar-free, and, as one can readily believe, dumfounded her home doctor when he chanced to see her eat her noonday meal. Her diet was arranged with design and was of extraordinary simplicity. It consisted of oatmeal, 60 grams; orange, 200 grams; eggs, 3; 20 per cent. cream 120 grams.

An early case that surprised us by failing to respond well, was that of a young girl, Case No. 2801, with an enlarged adolescent thyroid gland. Diabetes had developed acutely on June 27, 1922, been recognized on July 26, and on July 28, the patient came for treatment showing 6 per cent. of sugar and ++++ acidosis. The metabolism was high (Oct. 7, 1922), being +17 per cent. when compared with the Girl Scout group and —20 per cent. on the DuBois scale. Various methods of dieting were unsuccessful, but with insulin the patient has gained from 82 pounds to 95 pounds in the course of 43 days, though for the entire period of treatment she has lost weight. However, 45 units are required daily to enable the patient to utilize carbohydrate 35 grams, protein 61 grams, fat 138 grams, calories, 1626. This patient is cited elsewhere as an example of the danger of the withdrawal of insulin.

Another early juvenile case, stubborn without insulin, hopeful with, was Alice S., Case No. 2802, 15 years of age, who resisted treatment by undernutrition during two weeks. The outlook appeared very grave. Insulin was started, and at once improvement began. From the first day of her entrance to the hospital she had cooperated to the utmost with the efforts made in her favor, and it is no surprise that with the help insulin gave she should have done remarkably well. Upon admission on August 11, 1922, which was 5 months after onset of diabetes, her weight was 67.5 pounds. When insulin was begun, the weight was 66.3 pounds. She left the hospital on November 2, 1922, weighing 69.3 pounds, and at present she shows a gain from the lowest weight, after insulin was started, of 21.3 pounds. This little girl now weighs more than she ever has in her life, regulates her own diet, and carries out her own treatment with the help of her mother. *She lives in a country town 150 miles from the hospital. This long distance her old, overworked, country doctor traveled in order to see for himself the effect of insulin and its administration and to take her home. We have had no cooperation in doctor and patient greater than this.*

Betty C., Case No. 2931, a little girl of 5 years, entered the Corey Hill Hospital with severe acidosis on November 29, 1922, with onset the day before. With a rearrangement of diet and a total of 42 units of insulin she left the hospital eighteen days later sugar-free, taking carbohydrate 58 grams, protein 40 grams, fat 69 grams, 59 calories per kilogram body weight and has continued to remain sugar-free.

Mrs. C., Case No. 2948, was a woman of 28 years with onset in June, 1922, who entered the hospital on December 5, 1922. She reached a diet without insulin of carbohydrate, 33 grams, protein, 56 grams, fat, 105 grams. This was insufficient, and in consequence 302 units of insulin were given and she was discharged on December 31, 1922. Reporting on January 19, 1923, she states she is taking 12 units of insulin daily, weighs 108 pounds, representing a gain of 3.5 pounds, 4.1 per cent. above her lowest hospital weight. Her diet consists of carbohydrate, 44 grams; protein, 55 grams; fat, 123 grams; calories, 1603.

Mr. Francis C., Case No. 2946, entered the hospital and remained a few days during which he was given insulin. On account of home worries he left the hospital December 22, broke treatment, and returned 33 days later, on January 24, 1923. During the subsequent 6 days the urine, which contained 6 per cent. of sugar on entrance, has become sugar-free, his calories are 1415, and the total number of units taken during these days has been 85. No such results could have been obtained formerly at our hands without insulin.

From these cases of diabetes of short duration one can simply conclude that insulin has worked favorably, that the patients have shown an unusual gain in weight, and become sugar-free more readily than is customary.

The keenest professional happiness of all has been to watch the return to activity of some of the frail but faithful patients who have been under my care for many years.

The oldest of these is Colonel P., Case No. 632. This patient developed diabetes ten years ago, and has been reported in detail elsewhere. On account of his remarkable record he was not brought back for treatment until November 28. At that time he was living, as had been the case for many months and almost years, upon carbohydrate 15 grams; protein, 69 grams; fat, 103 grams. Various tests were first made with levulose and dextrose for comparison with similar tests conducted with this same subject in 1917 and now in press.[1] The more recent series of tests will be reported in detail elsewhere. Following 8 units of insulin per day and levulose, the diet of this patient has been increased from carbohydrate 15 grams to carbohydrate 43 grams, and the total calories from 1263 to 1795. In the forty-seven days of treatment the weight has increased 5 pounds, 4 per cent. from the lowest recorded pounds, and probably would have increased more had it not been for an infection which occurred after he went home.

Mr. B., Case No. 705, age 66, who developed diabetes 14 years ago, was first seen by us on Feb. 28, 1914. He entered the hospital Nov. 16, 1922, received 28 units in the course of 6 days, and died in the hospital of angina pectoris. Death occurred in the early morning hours and could not in any way be attributed to insulin. The importance of the case merits the inclusion of the hospital chart. The possible relationship of undernutrition, lowered blood pressure and blood volume to coronary occlusion, must be considered.

TABLE V

Death from Angina Pectoris in a Diabetic 66 Years of Age

Date	Urine				Diet				Blood Sugar	Insulin (Units)
	Vol.	Diacetic	Sugar		C	P	F	Cals.		
1922	c.c.		%	gm.	gm.	gm.	gm.			
Nov. 16	....	0	2.2	24	..	..	..	....	....	..
Nov. 17	2400	0	0.5	12	65	28	26	606	0.18	2
Nov. 18	1300	0	0.4	5	35	33	56	776	....	4
Nov. 19	1900	0	0.3	6	35	33	56	776	....	4
Nov. 20	2200	0	0.2	7	40	49	78	1058	....	6
Nov. 21	1000	0	0.2	2	40	57	83	1135	....	6
Nov. 22	....	..	...	..	44	65	99	1327	....	6

Mr. P., Case No. 866, has had diabetes nine years and has been a visitor at the Deaconess Hospital since May 21, 1915. Repeated data upon this patient have been published. When he returned for treatment with insulin on October 13, 1922, he was 50 per cent. under normal standard weight. It was felt that the improvement which some other patients had shown with insulin, who were nearly as much below weight, might have been due to their extreme undernutrition and that if they had simply been given food without insulin they might have done fully as well. With this most reliable patient, an agreement was made, by which his diet should be increased without insulin the same as that of Miss M., Case No. 1542, who was 44 per cent. under standard weight at her commencement of insulin treatment. This was done, and the results are shown in Table 6.

TABLE VI

Effect of Increase in Diet After Long-Continued Undernutrition—No Insulin

Mr. P., Case No. 866

Date	Diacetic Acid	Sugar in Urine	Average Daily Diet				Blood Sugar (F.)	
			C	P	F	Cals.	Date	%
October		gm.						
14–24 inc.	0	0	31	74	75	1095	Oct. 22	0.13
25–31 inc.	0	0	36	84	79	1191	Oct. 30	0.14
31–Nov. 5 inc.	0	0	43	86	86	1290	Nov. 6	0.19

It will be seen that Mr. P. really did not begin to show sugar in the urine after his diet was increased until fourteen days had elapsed, and the blood sugar did not rise notably until the end of thirteen days. Then, however, it had reached a considerable figure, 0.19 per cent. His case demonstrated clearly that even an undernourished patient cannot, with

impunity, raise his diet. With insulin the blood sugar fell, the diet was maintained at the higher level, and the patient has gained 3 pounds in weight in sixty-nine days, following his 3 weeks of increased diet without insulin. Unfortunately his life outside the hospital is in unfavorable surroundings.

Insulin is as useful in a surgical emergency of a diabetic of eleven years' duration, as in a case of one year's duration. Mrs. D., Case No. 1245, has had diabetes eleven years. She developed a carbuncle and later a second carbuncle which required an incision 10 inches long. With the help of 37.5 c. c. (not units) in 23 doses and with the surgical assistance of Dr. R. C. Cochrane her acidosis disappeared, she became sugar-free and remained so. Insulin was taken for 20 days only and has not been employed for the past eighteen weeks. She reports herself to be sugar-free and free from acidosis.

Mr. P., Case No. 2148, had diabetes of thirteen years' duration complicated by cirrhosis of the liver. He had steadily lost ground for over a year, occasionally developing ascites. Insulin was used, not only for humanitarian reasons but to determine whether in a patient with cirrhosis it would act. This was found to be true, because the patient became sugar-free on a diet which he could not previously take. Subsequently he developed pulmonary tuberculosis, and, as is frequent when a patient develops tuberculosis and it is advancing, his tolerance for carbohydrate rose, and reached 76 grams. He succumbed to tuberculosis on October 26, 1922. During the last few weeks of his life insulin was omitted, because it was obviously not needed.

The futility of giving insulin to an ignorant and unappreciative patient is illustrated by Mrs. M., Case No. 2853, who had diabetes of ten years' duration, and was admitted on account of an infection of the foot of many months' duration. She did not become sugar-free during 14 days in the hospital, though the glycosuria fell from 6.6 per cent. to 0.3 per cent. In this period she received 58 units of insulin. She was an Italian, weight 144 pounds, understood no English, and left the hospital on a diet of 22 calories per kilogram body weight with the foot nearly healed. No interest in dietetic treatmert or in treatment by insulin could be evoked in her or in her physician, though some cooperation was obtained in her family.

Mrs. R., Case No. 2201, a patient sixty-three years of age, has a tolerance of 90 grams carbohydrate and 1486 calories. The blood sugar varied in two weeks between 0.14 and 0.16 per cent. On account of progressive disturbances in the eye with blindness before her it was decided to give her insulin. No harmful effects have been noted and, aside from improved morale, no change in her condition has been observed, but the interval in which she has taken insulin has been short.

Our experience with cases of diabetes of varying duration, ranging from six weeks to over twenty years, demonstrates that the effects of insulin are independent of the duration of the disease.

Dosage

With the first cases in early August the dosage was small for two reasons: first, because we were unacquainted with insulin; and second, because we had little of it and wished to give it to as many patients as possible, so as to prolong their lives. So many cases have gathered around this clinic in the last 24 years, he would be hard-hearted indeed who endeavored to give much to one case when a little to several would enable them to live enough longer to get the advantage of the increased supply of insulin.

The greatest number of units given in any one day was to Mr. C., Case No. 2446, who died within 18 hours after admission to the hospital of pneumonia in the gray hepatization stage, as proven by the autopsy. This man received 100 units. His blood sugar increased from 0.41 to 0.57 per cent., the sugar in the urine remained the same, 2.8 per cent., and the CO_2 capacity of the plasma increased from 21 vols. per cent. to 33 vols. per cent.

Case No. 2256 has taken at times 63 units a day. Case No. 2801 has taken 45 units. On a few occasions Miss M., Case No. 1542, has received 30 units. Case No. 2687 also has taken over 20 units daily on 83 days. With these exceptions none of the 83 patients have received over 20 units a day. It is obvious that our early patients received too little, but the reasons therefor have been explained. Whether our present patients should receive more is a question. The factor of expense for these patients, most of whom are in moderate circumstances, must not be disregarded. It is obviously unfair to treat a patient with large doses of insulin in the hospital without cost, and then to send the same patient home expecting him to pay for that dosage of insulin indefinitely. The factor of expense has been carefully considered by us, and though we have been furnished most generously with insulin by the Eli Lilly Company, and though they have assumed several patients who have undergone special tests in the early stages of the development of insulin (iletin, Lilly), one cannot expect insulin to be furnished to many patients without cost. In fact, we believe that the sale of insulin will be a boon rather than a detriment to our patients and to insulin therapy in general. When a patient pays for insulin, he is sure to make careful determinations as to the method in which it can be employed to the greatest advantage. Patients learn whether carbohydrate should be increased at this meal or decreased at another with surprising

readiness, and their adjustment of their own dose is often far better than that of a physician, who seldom is familiar with all their conditions of life.

The advantage of small doses must also be emphasized. It is possible that with returning strength of the patients and increasing metabolism these doses will need to be increased, but if so, such increase has been gratifyingly slow in a large group of these patients. As a rule, such patients have been children in the early stages of diabetes.

The power of insulin to enable the body to utilize carbohydrate in diabetes is largely independent of body weight, despite the close relation to weight which has been found to exist between insulin and the weights of rabbits used for its standardization. In this respect it acts quite differently from the standard drugs. A baby of 10 pounds may require as much insulin as an adult weighing nearly 200 pounds, because of deficiency of pancreatic hormone. Although reason teaches us that this should be true, it is nevertheless hard to believe, and it still remains a wonder that this limpid liquid injected under the skin twice a day can metamorphose a frail baby, child, adult, or old man or woman to their nearly normal counterparts.

When insulin is administered before breakfast and before supper and fails to keep the patient free from sugar, an additional dose before the noon meal will bring this about. We have not enough data at hand to say yet, whether a given number of units in 2 doses before 2 meals will accomplish as much as the same number of units taken before 3 meals. It is obviously less trouble to take insulin twice a day, and though often at the hospital in order to avoid possible reactions, insulin in the first days of treatment is administered 3 times a day, gradually toward the end of hospital stay the dosage has been changed to twice a day, especially at the suggestion of Dr. Banting. Time will undoubtedly soon show what is the best method of dividing the meals and dosage. Nor can definite rules be laid down for the time at which insulin should be administered. Usually it appears to act more efficaciously if given from three-quarters to one-quarter of an hour before a meal, but there are patients with whom better results are obtained if it is given one and one-half hours before a meal.

Must the Dosage of Insulin be Increased?

We are unwilling to express an opinion at the present writing. In the first place there are two separate possibilities: progressive severity of the diabetes which of itself demands more insulin, and secondly, the disease stationary but the insulin losing effect.

In a recent publication Allen and Sherrill[4] have adduced new evidence for the conclusion already advanced in earlier publications by Allen that diabetes is not a progressive disease. Unfortunately their evidence is not entirely satisfactory, and experiences with our own patients make us hesitate to accept what we should like to believe. It is true that cases like Colonel P., Case No. 632, and Mary G., Case No. 1949, who have followed dietetic rules with scrupulous fidelity, have shown extremely slight downward progress, but we believe both these patients and their relatives would agree that they are not as well now as two years ago. If, therefore, one must regretfully consider that even under the best of dietetic conditions there is some progress in the disease, one can expect the necessity of increasing the dosage of insulin in the course of years. Miss M., Case No. 1542, who has been under treatment since August seventh, has rather more difficulty in keeping free from glycosuria with 20 units today than she did some months ago. Whether the same difficulty would exist if she were living under exactly the same conditions as five months ago is open to question. Another factor enters in here which will now be discussed more in detail.

The recompense for long subnutrition is often not recognized in estimating the value of insulin. At the beginning of treatment a false value is often ascribed to the unit, particularly in long-standing, carefully treated diabetics. These patients are like Mr. P., Case No. 866, who was 50 per cent. under standard weight, and had been undernourished so long that it required upwards of three weeks for him, even without insulin, to develop sugar in the urine, although 327 calories were added to his diet. Therefore, when one gives a unit of insulin to a patient of this type, undue worth may be ascribed to it.

An unwarranted preciseness is also often attributed to insulin unitage. Experience makes clear that despite the earnest efforts of the manufacturers this ideal is only gradually being attained.

In view of these two as yet unmeasurable variables it will require weeks or months, perhaps years, of experience with

insulin and with these patients before one can conclude that the dose of insulin must be increased to produce the same results. In the discussion of the changes in the metabolism of diabetic patients before and after treatment with insulin, as shown in Table 9, one can see how materially the aspect of these patients has altered. Thus, of 11 cases, the basal metabolism on the average was 1017 calories before insulin was begun and after an average period of 63 days with insulin treatment it had risen to 1113 calories. One is dealing with two different types of diabetic individuals, the diabetic with the subnormal metabolism, which we have all treated since the introduction of fasting in 1914, and now with a diabetic with nearly normal metabolism. Let us be careful in our enthusiasm not to produce the diabetic of increased metabolism so frequently in evidence between 1908 and 1914.[3] No one yet is quite sure of the optimum metabolism of the diabetic.

As to the second possibility,—namely, the failure of the body to react to insulin,—little can be said. It is true that save for 6 emergency cases in which insulin has been employed the tendency has been to give more, rather than less, insulin as months have gone by. We believe that this can be explained better by the change in the metabolism of the patient than by diminution in the power of insulin to act. Six months from now more definite results can be furnished. To be on the safe side we prefer to give five, ten, fifteen, or twenty units of insulin, so that in case of necessity we can double or treble the dose rather than to give larger doses at the start.

The true value of a unit of insulin can be more easily determined in a patient whose undernutrition is slight and whose diet has been at a constant level than in the undernourished patient. Particular care must be exercised in avoiding conclusions upon the dosage of insulin in patients whose diets are changing from day to day. It must be remembered that probably ninety per cent. of all diabetic patients will become sugar-free after they follow the test diets which we are accustomed to use with our patients when they first enter the hospital. Insulin given on any of these days might lead to erroneous conclusions. Frequently patients will become sugar-free upon these diets, rapidly working up to nearly 30 calories per kilogram body weight and carbohydrate 100 grams, but after remaining at this level for three or more days, will show a return of sugar. Our experience in metabolism

tests during which patients have taken 1.5 grams levulose, sucrose, dextrose, or carbohydrate in other forms per kilogram body weight has taught us to be very slow and cautious before judging of the tolerance of a patient for carbohydrate during a period of one or two days. The beautiful table of Wilder, Boothby, and Beeler also shows this.[5] With their patient, Bessie B., the effect of the diet only reached its maximum on the last day of the period upon which it was taken. In other words, for scientific interpretation of insulin effect we require a fore-period of nearly a week on an unchanged diet, and this requirement is not always consonant with the individual patient's interest.

Reactions

Thirty reactions have occurred in the course of 5,153 doses of insulin in hospital. These took place with 11 patients. Outside of the hospital reactions have been reported by five patients. The policy cited of giving few units accounts for the scarcity of reactions. Whether we should have risked more reactions is yet to be determined. Undoubtedly with more insulin more food can be taken and more weight gained, but the reasons for proceeding slowly have already been stated.

The reactions have seldom been alarming. They were most severe with three little boys, Freddie G., Jack K., and Philip S.

(1) Freddie G. was drowsy, listless, and perspired for three hours although he received 100 grams orange at its first appearance, then had his dinner, and finally recovered only after a second dose of 50 grams of orange. The urine remained sugar-free, and the blood sugar was 0.058 per cent. This little boy had in all eleven reactions and we were suspicious that he feigned a reaction in order to get food, until we found that invariably a reaction was accompanied by a low blood sugar. The percentages were as follows: 0.06, 0.07, 0.09, 0.058, 0.036, and 0.04. (2) Jack K. had three reactions of which one was alarming. He was found on the floor cyanotic, nearly unconscious, but recovered with orange juice. No delirium or excitement was observed. (3) Philip S. was also found unconscious and perspiring, but promptly recovered.

The symptoms of a reaction were those which have been already described by the Toronto workers; sudden hunger, slight flushing of the face, perspiration, the subjective sense of tremor, as well as actual trembling, (Aune N.'s spoon shook as she ate her oatmeal). The facies was characteristic: marked pallor, though the lips might be cyanotic, the eyes sunken, with perspiration which was most marked upon the forehead, cheek-bones, and upper lip. The palms and forearms were also especially moist. The facial muscles are often completely relaxed as in complete exhaustion.

The patients sometimes complained of "stomach and intestines being flattened upon the backbone and passing of gas by rectum." The desire for evacuation of the bowels occurred.

Blood sugar determinations were made at the moment of suspicious symptoms in 11 instances. These varied from 0.036 to 0.08 per cent.

An old lady, Mrs. L., Case No. 2716, was in the hospital at this period and though not an insulin case gave a blood sugar test, following a sharp restriction of diet, of 0.03 per cent. In her case the reliability of the determination was fully checked by 3 observers. Although Mrs. L. had no characteristic reaction she felt that she was dying and actually was too weak to feed herself. Her pulse was thin and rapid and only after frequent feedings with oatmeal gruel did she recover.

With several patients, at other times, blood sugar values were obtained which were quite as low. With Freddie no reaction occurred after a blood sugar of 0.06 per cent. and with Alice S., Case No. 2802, none occurred when the blood sugar was as low as 0.04 per cent. An unexplained anomaly occurred on another occasion with this same child: she had what was thought to be a reaction and the blood sugar was 0.09 per cent., but this was at 3:45 P. M., which was 5¾ hours after three units of insulin, and nearly 4 hours after dinner. This delayed reaction, if such it be, may be one of those paradoxes that point out new paths of study.

The earliest period at which a reaction occurred after insulin was 15 minutes, and the latest period other than the case just cited three and three-quarters hours. Perhaps this late reaction is to be related to the amount of exercise which the patient in question took. At any rate he thought that a long walk tended to make him more liable to a reaction. It is important to know how late a reaction can come on after insulin, especially with children who go to bed early and within 2 hours of their evening meal. Freddie showed such a reaction at 7:30 P. M. which was 3½ hours after his evening dose of insulin.

The danger of a single unit may easily be overlooked. So many patients take so many units that a single unit seems harmless. It is not.

Mr. K., Case No. 2909, came many miles with many letters beseeching insulin. Diet and diarrhea, the latter of 9 months' duration, *not* beginning in the hospital, reduced the urinary sugar from 6 per cent. to zero in 3 days, and his tolerance rose to C 114 grams, P 65 grams, F 79 grams. He literally longed for insulin. We yielded and gave him 2 units and his blood sugar fell to 0.04 per cent. within 1 hour. Not completely satisfied, two days later one unit was given and his blood sugar in 2 hours was 0.03 per cent. When he was told that he was one of two patients whom up to that time we had seen live despite so low a blood sugar, he was content to go without it.

It must be borne in mind that reactions may occur when the carbohydrate in the diet is high for a diabetic.

H. H., Case No. 1889, while taking 61-92 grams of carbohydrate and 20 units of insulin showed reactions on 4 occasions. Case No. 2909, although he had no subjective reaction, had a fall in blood sugar to 0.04 per cent. after one unit of insulin and 81 grams of carbohydrate in the diet. Patients are often very clever in adjusting their diet and their insulin. Case No. 1889 found that a little sugar occurred in his afternoon urinary specimen and that he had a slight reaction in the forenoons. He made a slight shift in his carbohydrate, prevented the reaction and banished his glycosuria. Incidentally this illustrates a new field of utility for the wider use of selected specimens of urine, urged from this clinic by Gray.[6]

The time at which insulin is given in relation to the taking of food is important. It varies from patient to patient. At one period our cases appeared to do better when they had insulin an hour or even an hour and a half before a meal, and this is still true with one patient, but recently the results seem more efficacious when the insulin is taken within three-quarters of an hour of the meal. No optimum interval appears to exist for all patients, or even for the same patient at all times. The character of the meal determines to a considerable extent its rapidity of absorption, and upon this must necessarily depend the need of insulin. In general, however, it can be said that it is safer for insulin to be followed by food within the subsequent half-hour. Particularly is this of importance if one desires to get a maximum effect, in order that the peak of the curve of activity of insulin may correspond with the peak of the curve of the blood sugar.

Protein Reactions

Protein reactions, as distinct from general reactions, have occurred with four patients and only three in the hospital. Case No. 2802 developed urticarial wheals with pruritus, which was relieved by bathing with sodium bicarbonate and "white wash." In two other patients urticaria was reported, and a fourth reports that a similar condition developed at home.

Abscesses

No abscesses developed as a result of injections of insulin. The number of injections given in the hospital was over 5,100 between August 7 and January 18. There have very frequently been indurations at the site of injections and in one patient there was a small crusted ulcer without evidence of infection which possibly might have been the result of a burn from tricresol.

The Blood Sugar

With children few blood sugar estimations are made in the institutions where our patients are treated. In the remainder of the patients the blood sugar has been determined upon admission to the hospital, upon the disappearance of glycosuria, upon the diet reaching a high quantity of carbohydrate, 100 grams more or less, even without the appearance of glycosuria, also in reactions after insulin and during any symptoms suggesting a reaction, and shortly before discharge. The energies of the laboratory have been concentrated upon studies of the blood in connection with various observations upon the metabolism of diabetics, some of which are here reported. Fortunately for our peace of mind we are not of those who have held that the blood sugar in diabetes must be kept at a normal level at all hazards. Too many patients have crossed our path who have resisted diabetes for many years with elevated percentages of sugar in the blood to allow us to accept such an extreme view. The maintenance of the patient upon a normal blood sugar is seldom attained with insulin. Insulin allows more food and enables its utilization to take place, but in the intervening hours before the next dose the blood sugar rises higher than is customary with the undernutrition diet.

Rapidity of action of insulin: Most reactions with hypoglycemia occurred within 1-1½ hours of its administration. In some instances the blood sugar remained at low level during the greater part of the day, even though carbohydrate food was taken, e. g., Alice S., 0.04 per cent. fasting at 8 A. M., 0.09 per cent. at 3:45 P. M. But in general with patients who are receiving a diet considerably in excess of their own unaided metabolic power to utilize, the rise of blood sugar after the fall is equally rapid. Hence periods of glycosuria alternate with periods of aglycosuria. The inconvenience of frequent injections limits the number to one or two daily. Therefore, every effort to prevent wide fluctuations in blood sugar should be made by concentrating the carbohydrate portions of the diet at the meal following injections and by separating the injections during the day by long intervals. Following a visit of Dr. Banting we changed the breakfast of several patients to 7 A. M. and their evening meal to 6:30 P. M. with distinct benefit.

Patients with long-standing hyperglycemia may be more resistant to insulin, especially when infection is present, as was

observed with Case No. 2446, Table 22, who died of pneumonia. Probably blood volume and the total amount of circulating sugar is important. Thus, reactions were most frequent with the emaciated little mite, Freddie G., and a reaction occurred with a single unit with Mr. K., Case No. 2909, exhausted with diarrhea.

Two patients, Case Nos. 2448 and 2853 had symptoms suggesting reactions, but their blood sugars at the time were 0.27 per cent. and 0.24 per cent. It may be that the symptoms are due in some instances to a rapid fall, even of a few points and not to true hypoglycemia. *The blood sugar is essential in recognizing the true hypoglycemic reaction.*

Blood Volume. The loss of fluid and extreme emaciation with reduction of blood volume, resulting from diarrhea, may be a factor in such cases as that of Mr. K., just cited, with whom a small dose of insulin produced hypoglycemia. *If* insulin does act as a chemical agent to force oxidation of glucose, then the relation of the amount injected to the amount of oxidation required must be of importance in determining the amount of reduction of the blood sugar. At any rate, the question of blood volume in relation to insulin needs investigation.

The practical importance of the relationship between blood volume, total circulating glucose, and the insulin dose was illustrated in the case of a scientist, Case No. 2383. Absolutely faithful to diet and careful in measurement, there is little chance of dietary error as an explanation of the following phenomenon. He had been taking carbohydrate, 70 grams; protein, 80 grams; fat, 135 grams; and had had regularly 3 units insulin in the morning. On one occasion he had an extremely copious and watery movement in the early morning; in fact, almost a diarrhea. At 11 A. M. he had sudden intense hunger, so severe that he almost phoned to us in panic. However, it passed off in half an hour. The moral is plain. Patients in hospital or home may experience dangerous hypoglycemic effects from a dose of insulin, ordinarily safe, in the presence of a temporary diarrhea or other factor lessening blood volume and total glucose in the blood.

Dangerous hypoglycemia may occur without warning symptoms. A typical reaction may occur without extreme hypoglycemia. Children and patients weakened and desiccated, especially by diarrhea, and in general all patients, should be given insulin with the assumption that a dangerous hypoglycemia may occur with any dose.

Blood Fat

Our data upon the changes in the fat of the blood of diabetics are not numerous. Mr. C., Case No. 2448, showed a fall in percentage of total fat in the blood from 2.28 per cent. on October 17 to 0.94 per cent. on November 6. The urinary findings, the diet, and dosage of insulin during this period are given in Table No. 7.

TABLE VII
Blood Fat.
Case No. 2448.

Date	Diacetic Acid	Sugar in Urine		Diet				Blood Fat Bloor	Insulin
				C	P	F	Cals.		
1922		%	gm.	gm.	gm.	gm.		%	units
Oct. 18.....	++	6.5	169	110	18	0	512	2.28	8
Oct. 20.....	++	2.4	82	64	29	19	543	1.74	12
Oct. 23.....	sl.+	0.3	5	3	2	0	20	1.56	16
Oct. 26.....	0	0	0	17	27	52	644	1.50	16
Oct. 30.....	0	0	0	55	51	68	1036	1.57	16
Nov. 6.....	0	0	0	67	66	106	1486	0.94	16

Note: The diet, urinalyses, and insulin dosage are given for the 24 hours preceding the date of the fat determination.

The change in the blood fat in the case of Miss M., Case No. 1542, who has been longest under treatment is also striking. On August 2, 1922, the fat in the blood was 3.18 per cent. and on November 6, 1922, it was 0.67 per cent.

Metabolism

The basal metabolism and respiratory quotient were determined in a group of 11 patients at the beginning of their treatment with insulin and again after an interval of 18 to 111 days. The average basal calories of these 11 patients before insulin medication was 1017 and after insulin medication 1113, an increase of 9.4 per cent. All the patients but 3 showed a material increase in basal metabolism. With these 3 cases the basal metabolism varied less than 14 calories at the two periods. The greatest increase in basal metabolism was with Case No. 2801, who showed a gain of 262 calories in 88 days, or 24 per cent., with a gain in weight in the same period of 4 per cent.

The patient with the lowest metabolism in the series of the patients taking insulin and of the entire series of patients studied at the New Eng-

TABLE VIII

Blood Fat.

Case No. 1542

Date	Di-acetic Acid	Sugar		Diet				Blood Fat Bloor	Insulin
				C	P	F	Cals.		
		%	gm.	gm.	gm.	gm.		%	c.c.
1922									
Aug. 2	+	1.4	59	13	26	82	894	3.18	0
Aug. 7	+	0.8	22	13	26	82	894	1.72	0
Aug. 9	+	1.4	46	24	29	83	959	2.82	0.6
Aug. 11	+	1.1	47	24	29	83	959	2.20	2.0
Aug. 14	+	1.0	40	24	29	83	959	3.00	0
Aug. 18	sl.+	0.5	20	24	29	89	1061	1.46	4.0
Aug. 28	0	0.6	35	33	37	96	1144	1.80	0
Sept. 5	0	0.2	11	33	45	99	1203	1.70	4.0 units
Oct. 2	0	0.6	30	33	45	101	1221	0.76	6
Oct. 11	0	0.4	18	22	30	68	820	0.89	12
Oct. 23	0	0	0	14	32	98	1066	0.88	16
Nov. 6	0	tr.	0	16	33	98	1078	0.67	20

Note: The diet, urinalyses, and insulin dosage are given for the 24 hours preceding the date of the fat determination.

land Deaconess Hospital and Nutrition Laboratory, and, in fact, in the literature upon diabetes, was Mr. P., Case No. 866. His diabetes was of 8¾ years' duration. His weight fell to 50 per cent. below normal standard. On October 14 and 16 his basal metabolism was 854 and 749 calories, respectively; in other words, —33 and —43 per cent., by the Harris and Benedict standard. These values were well supported by values for the ensuing three weeks. Ten weeks later the metabolism showed a material gain, but he still is 26 per cent. below the normal level.

In Table 11 the basal metabolism of Case No. 2801 is shown for 7 observations between October 7 and January 15. The favorable rise at the beginning of treatment is brought out and the uniformity of the results early in the course of treatment and at the end. In this patient there was a fairly steady gain in metabolism upon successive days and the respiratory quotient rose as well. The basal metabolism of the patient on October 7 was —20 per cent. and finally came to as near normal as —5 per cent. on January 15.

The immediate effect of insulin on the basal metabolism and respiratory quotient was determined with Case No. 2448. This patient received, following the determination of the basal metabolism, 6 units of insulin. During the subsequent two hours and forty-six minutes the blood sugar fell from 0.28 per cent. to 0.22 per cent., but neither the metabolism nor the respiratory quotient showed a consistent change. What would have happened if the dose of insulin had been larger is therefore open to conjecture.

TABLE IX

Basal Metabolism and Respiratory Quotient of Diabetic Patients Before and After Treatment With Insulin

Case No.	Date Before Treatment	No. of Days Treated	Age	Height (Net)	Weight (Net)	Gain in Weight		Calories Per 24 Hours		Gain in Calories		R. Q.		Blood Sugar (F.)	
						Actual	Per Cent.	Before	After	Actual	Per Cent.	Before	After	Before	After
	1922		yr.	cm.	kg.	kg.	%	cals.	cals.	cals.	%			%	%
632	Dec. 1	18	41	177	49.6	0.3	0.6	1115	1186	71	6.4	0.76	0.79	0.14	0.13
866	Oct. 14	101	39	186	39.9	3.1	7.8	854	977	123	14.4	0.80	0.81	0.12	0.17
1542	Oct. 4	111	42	164	33.6	2.6	7.7	903	1033	130	14.4	0.78	0.76	0.31	0.26
1889	Nov. 13	68	17	156	28.4	2.9	10.2	849	1031	182	21.4	0.86	0.83	0.16	0.20
1970	Dec. 4	51	52	156	51.7	0.5	1.0	1198	1204	6	0.5	0.83	0.78	0.24	0.20
2256	Nov. 9	98	18	165	23.1	3.4	14.7	821	887	66	8.0	0.76	0.78	0.31	0.19
2448	Oct. 20	52	19	172	43.5	6.3	14.5	1355	1341	−14	−1.0	0.76	0.82	0.28	0.14
2687	Dec. 11	37	25	164	43.2	−0.1	−0.2	1119	1303	184	16.4	0.75	0.83	0.24	0.27
2729	Nov. 7	35	22	181	48.2	0.8	1.7	954	1012	58	6.1	0.78	0.81	0.22	0.14
2801	Oct. 19	88	15	161	38.0	1.5	4.0	1090	1352	262	24.0	0.76	0.79	0.35	0.39
2972	Dec. 21	34	67	151	33.7	2.1	6.2	931	921	−10	−1.1	0.79	0.75	0.25	0.22
Averages						2.1	6.2	1017	1113	96	10.0 3	0.78	0.80	0.24	0.21

TABLE X

Basal Metabolism of Case No. 866 Before and After Treatment with Insulin [1]

Date	Age	Height (Net)	Weight (Net)	Oxygen Consumed per Minute	Carbon Dioxide Eliminated per Minute	R. Q.	Computed Calories per 24 Hours	±% Variation from Standard (H. & B)
1922	yrs.	cm.	kg.	c.c.	c.c.		Cals.	%
Oct. 14	39	186	39.9	124	99	0.79	854	−33
Oct. 16	39	186	42.1	108	87	0.81	749	−43
Oct. 23	39	186	42.9	124	100	0.80	857	−35
Oct. 25	39	186	41.6	122	97	0.78	840	−36
Oct. 30	39	186	41.8	124	102	0.83	864	−34
Nov. 6	39	186	41.5	125	105	0.84	873	−33
Nov. 10	39	186	41.8	130	106	0.81	901	−31
Nov. 24	39	186	42.5	135	111	0.82	938	−29
Dec. 12	39	186	42.6	139	111	0.80	961	−27
Dec. 15	39	186	42.8	148	116	0.79	1021	−22
1923								
Jan. 23	39	186	43.0	141	114	081	977	−26

[1] Treatment with Insulin begun Nov. 11, 1922.

TABLE XI

Basal Metabolism of Case No. 2801 During Treatment with Insulin

Date	Age	Height (Net)	Weight (Net)	Oxygen Consumed per Minute	Carbon Dioxide Eliminated per Minute	R. Q.	Computed Calories per 24 Hours	±% Variation from Standard (Du Bois)
1922	yrs.	cm.	kg.	c.c.	c.c.		cals.	%
Oct. 7	15	161	39.3	167	118	0.71	1128	−20
Oct. 10	15	161	38.9	158	112	0.71	1067	−24
Oct. 19	15	161	38.0	161	116	0.72	1090	−21
Oct. 24	15	161	38.6	158	116	0.74	1079	−22
Dec. 29	15	161	38.4	186	140	0.75	1269	− 8
1923								
Jan. 2	16	161	38.1	179	130	0.73	1215	−11
Jan. 15	16	161	39.5	196	147	0.75	1338	− 5

[1] Treatment with Insulin begun in August, 1922

The effect of insulin apart from food was also determined with Case No. 2801. (Table 13.) Following the determination of the basal metabolism 15 units of insulin were given. In the following 56 minutes three observations of the metabolism were made. The variations from the basal metabolism and respiratory quotient were negligible. At the end of this time breakfast was taken, which contained carbohydrate, 8 grams; protein, 13 grams; fat, 34 grams. The metabolism at once rose, reaching a maximum of 14 per cent. at the end of 2 hours. The respiratory quotient also increased, but to a very moderate extent, the peak being but 0.04 over the basal. At noontime the patient again received 15 units of insulin, which was followed by a meal of carbohydrate, 18 grams; protein, 31 grams; and fat, 44 grams. As a result the metabolism rose steadily in the subsequent hour and twenty-eight minutes from +15 per cent. to +19 per cent., reaching a maximum of +21 per cent. The respiratory quotient

TABLE XII

Immediate Effect of Insulin on Basal Metabolism and Respiratory Quotient.
Oct. 20, 1922
Case No. 2448. Age, 19 yrs., Hgt., 172 cms., Wgt., 43.5 kgs.

Time	Oxygen Consumed Per Minute	Carbon Dioxide Eliminated Per Minute	R. Q.	Calories Per 24 Hours	Blood Sugar
Hrs. and mins.	c.c.	c.c.		cals.	%
Avg. Basal.....	198	150	0.76	1355	0.28
		6 Units Insulin.			
12′ p. Insulin.....	208	143	0.69	1406	....
23′ p. Insulin.....	209	147	0.70	1410	....
1° 0′ p. Insulin.....	198	143	0.72	1339	....
1° 10′ p. Insulin.....	197	139	0.71	1329	0.24
1° 50′ p. Insulin.....	203	151	0.75	1384	....
2° 0′ p. Insulin.....	196	139	0.71	1321	....
2° 36′ p. Insulin.....	190	131	0.69	1285	.... 3°
2° 46′ p. Insulin.....	198	145	0.73	1345	0.22
Avg.....	200	142	0.71	1352	

TABLE XIII

Effect of Insulin Upon the Metabolism and Respiratory Quotient of Case No. 2801 Without and With Food. Jan. 2, 1923
Case No. 2801. Age, 16 yrs.; Hgt., 161 cms.; Wgt., 38.1 kgs.

Time	Oxygen Consumed Per Minute	Carbon Dioxide Eliminated Per Minute	R. Q.	Calories Per 24 Hours	Per Cent. Increase	Blood Sugar
Hrs. and mins.	c.c.	c.c.		cals.	%	%
Avg. Basal.....	179	130	0.73	1215	....	0.40
	15	Units of Insulin at		9.26 a. m.		
36′ p. Insulin..	177	123	0.70	1149		
46′ p. Insulin..	179	130	0.72	1212	− 2	.....
56′ p. Insulin..	176	131	0.74	1198		
			C P	F Cals.		
		Breakfast	8 13	34 390	at 10.55	a. m.
35′ p. Breakfast	194	143	0.74	1318	+ 9	.....
43′ p. Breakfast	192	146	0.76	1314	+ 8	.....
52′ p. Breakfast	195	146	0.75	1331	+10	..... 1° 12′
1° 2′ p. Breakfast	197	152	0.77	1349	+11	0.30
1° 52′ p. Breakfast	197	144	0.73	1336	+10	.....
2° 2′ p. Breakfast	202	156	0.77	1387	+14	.....
		15 Units Insulin at		1.19 p. m.		
			C P	F Cals.		
		Dinner	18 31	44 592	at 1.54	p. m.
1° 8′ p. Dinner..	207	146	0.71	1397	+15	.....
1° 18′ p. Dinner..	213	153	0.72	1440	+19	.....
1° 28′ p. Dinner..	217	158	0.73	1471	+21	.....

on the contrary fell. This patient, cited repeatedly in this article, was one of our severest cases.

To several individuals insulin was given and the metabolism thereafter immediately determined. This was followed by food and thereafter further observations made. Such a test is shown with Case No. 632, Table 14. With this patient, after a breakfast of carbohydrate 19, protein 22, and fat 53, the respiratory quotient rose 0.05, but the metabolism increased 24 per cent.

TABLE XIV

Effect of Food Upon the Metabolism and Respiratory Quotient in Severe Diabetes

Dec. 19, 1922

Case No. 632. Age 41 Years. Height 177 Cm. Weight 49.9 Kg.

Time	Oxygen Consumed per Minute	Carbon Dioxide Eliminated per Minute	R. Q.	Calories per 24 Hours	Per Cent Increase
Hours and Minutes	c.c.	c.c.		cals.	%
4 Units Insulin					
1[s] p. Insulin	172	136	0.79	1186	
C P F Cals.					
Breakfast 19 22 53 641					
31′ p. Breakfast	216	171	0.79		
41′ p. Breakfast	208	167	0.80	1469	24
50′ p. Breakfast	214	176	0.84		
1° 0′ p. Breakfast	211	171	0.81		

With case No. 2729, levulose was given on one day without insulin and on another with 12 units of insulin. The details of these tests are shown in Tables 15 and 16. On the day without insulin following the ingestion of 75 grams of levulose the basal metabolism rose to a maximum of 14 per cent. and the respiratory quotient rose from 0.77 to a maximum of 0.98 thirty-four minutes after levulose (Table 15). A similar observation was repeated 13 days later, save that 12 units of insulin were given the patient prior to his taking levulose (Table 16). Following the insulin and levulose the metabolism rose to a maximum of 19 per cent. and continued higher for a longer period than in the experiments without insulin. The respiratory quotient, on the other hand, did not rise quite as high after insulin as it did in the experiment without it, but it continued higher from about 1 hour after the insulin than in the other test. In this instance insulin failed to raise the respiratory quotient to as high a level as in the experiment without insulin, but the increase of metabolism when insulin and levulose were given together was greater.

In still another instance, Case No. 2448, insulin was given and was followed by a meal, and a few hours later insulin repeated and followed by another meal. With this patient the metabolism was determined 8 minutes after the insulin was first given. The calories found per twenty-four hours were 1171 and the respiratory quotient 0.81. Within half an hour after breakfast the metabolism had risen to 1415 calories, an increase of 21 per cent., and the respiratory quotient to 0.92, and a few minutes

TABLE XV

Effect of Levulose on Basal Metabolism. Nov. 7, 1922.

Case No. 2729. Age 22 yrs., Height 181 cms., Weight 48.2 kgs.

Time	Oxygen Consumed Per Minute	Carbon Dioxide Eliminated Per Minute	R. Q.	Calories Per 24 Hours	Per Cent. Increase	Blood Sugar
Hours and Minutes	c.c.	c.c.		cals.	%	%
Avg. Basal.....	139	107	0.77	954	....	0.22
		74.5 gm.	Levulose			
16′ p. Levulose.....	147	117	0.80	1014	+ 6	....
25′ p. Levulose.....	149	133	0.89	1054	+11	....
34′ p. Levulose.....	150	147	0.98	1083	+14	1°7′ 0.31
1° 18′ p. Levulose...	151	134	0.89	1069	+12	....
1° 27′ p. Levulose...	149	135	0.91	1057	+11	....
2° 16′ p. Levulose[1] ..	142	113	0.80	982	+ 3	2° 0.35
						3°12′
3° 41′ p. Levulose[1] ..	139	114	0.82	966	+ 1	0.34
						5° 50′
5° 35′ p. Levulose[1] ..	142	111	0.78	975	+ 2	0.28

[1]Average of two nine-minute periods.

TABLE XVI

Effect of Food Upon the Metabolism and Respiratory Quotient of Diabetic Patients With and Without Insulin.
Nov. 20, 1922.

Case No. 2729. Age 22 Years. Height 181 Cm. Weight 47.1 Kg.

Time	Oxygen Per Minute	Carbon Dioxide Per Minute	R. Q.	Calories Per 24 Hours	Per Cent. Increase	Blood Sugar
Hours and Minutes	c.c.	c.c.		cals.	%	%
Avg. Basal.....	143	113	0.79	986	..	0.21
	12 Units	Insulin and	73.5 gm.	Levulose	at 8.16	a.m.
21′ p. Ins. & Lev.	149	130	0.87	1046	6	....
30′ p. Ins. & Lev.	165	147	0.89	1168	19	....
39′ p. Ins. & Lev.	157	144	0.92	1118	13	....
48′ p. Ins. & Lev.	156	143	0.91	1112	13	....
57′ p. Ins. & Lev.	157	136	0.87	1106	12	1° 0.25
						2°
1° 31′ p. Ins. & Lev.[1]	151	145	0.96	1081	10	0.27
2° 41′ p. Ins. & Lev.[1]	149	131	0.88	1049	6	..
4° 2′ p. Ins. & Lev.[1]	145	126	0.87	1020	3	4° 0.24
						6°
5° 50′ p. Ins. & Lev.[1]	150	116	0.78	1031	5	0.20

[1]Average of two nine-minute periods.

later reached 0.95. One hour and ten minutes after breakfast a second dose of 8 units of insulin was injected. Following the second injection the respiratory quotient at first dropped to 0.81, but rose immediately to 0.94 and 0.89 at 1 hour and 27 minutes after the breakfast and eventually in

2 hours and 14 minutes reached 1.02 to fall again to 0.91. The increase in calories in this patient following the second injection of insulin was notable, amounting to 38 per cent. in contrast to 21 per cent. immediately after breakfast and the first injection of insulin.

TABLE XVII

Effect of Food Upon the Metabolism and Respiratory Quotient of Diabetic Patients, With and Without Insulin.

Case No. 2448. Age 19 Years. Height 172 Cm. Weight 47.5 Kg. Nov. 2, 1922

Time	Oxygen Consumed Per Minute	Carbon Dioxide Eliminated Per Minute	R. Q.	Calories Per 24 Hours	Per Cent. Increase
Hours and Minutes	c.c.	c.c.		Cals.	%
	8 Units Insulin 8 Mins. before Basal.				
Avg. Basal....	169	137	0.81	1171	..
	...	C P	F	Cals.	
	Breakfast	24 15	31	435	..
17′ p. Breakfast.....	199	182	0.92	1415	21
25′ p. Breakfast	...	...	0.95	....	..
	8 Units Insulin 1 hour after Breakfast.				
1° 10′ p. Breakfast..	233	189	0.81	1616	38
1° 19′ p. Breakfast.	198	187	0.94	1414	21
1° 27′ p. Breakfast.....	186	165	0.89	1314	12
2° 14′ p. Breakfast.....	206	209	1.02	1494	28
2° 23′ p. Breakfast.....	200	182	0.91	1423	22

ACIDOSIS

Insulin offers hope of greatly improving results of treatment in acidosis and coma.

Carolyn S., Case No. 2801, recovered from a severe acidosis, brought

TABLE XVIII

Recovery from Acidosis During 24 Hours Following Withdrawal of Insulin. Case No. 2801.

Insulin 3 Units Per Dose	Blood Sugar	Alveolar CO_2 Tension mm. /Hg.	Plasma CO_2 Tension mm. /Hg.	Urine		
				Time	Sugar gms. per hr.	Diacetic Acid
.....	.....	..	..	6.30—10.30 a.m.	6.3	++
7.50 a.m.	.....	24	..	10.30—12.30 p.m.	8.5	++
11.50 a.m.	.....	..	..	12.30— 2.30 p.m.	6.0	+
.....	0.35—12.50 p.m.	26	38	2.30— 4.30 p.m.	4.5	+
3.50 p.m.	.....	..	..	4.30— 6.30 p.m.	3.2	+
.....	0.37— 4.50 p.m.	31	..	6.30— 8.30 p.m.	2.6	sl+
.....	.....	28 5.30 p.m.	..	8.30—10.30 p.m.	3.3	sl+
7.50 p.m.	.....	..	.. —	10.30— 6.30 a.m.	0.6	sl+
.....	0.37— 9.50 p.m.	31	43	.....	...	....

on by withdrawal of insulin, within a few hours of resuming insulin. The following table shows her progress during twenty-four hours.

Helen Q., Case No. 2687, came to the hospital on November 27 on the verge of coma. An abscessed tooth had required operative drainage four days previously. Extreme nausea had prevented her taking any food for twenty-four hours. The following table shows her progress.

TABLE XIX

Disappearance of Acidosis with Insulin. Case No. 2687

Date	Diacetic Acid	Sugar in Urine		Alveolar Air	Blood Total Acetone	Blood CO_2 Vol. %	Blood Sugar	Diet in Gms.				Insulin Units
		%	gm.	mm/Hg.	mg. per 100 c.c.			C	P	F	Cals.	
Nov.												
27–10 p.m.	+++	2.5	....	17	....	30	0.45	....	....	....	....	....
27-28 (12 hr.)	++	2.6	31	....	....	....	.....	50	6	0	224	14
28-29	+	1.8	28	27	30.6	....	0.39–8 a.m. 0.34–5 p.m.	52	29	24	540	12
Dec.												
4- 5	++	1.3	22	....	....	....	0.30	24	51	97	1173	18
8- 9	++	0.4	5	36	....	....	.....	25	50	98	1181	22
11-12	0	....	....	....	....	....	0.24	27	51	103	1239	24
15-16	0	....	....	36	....	....	.....	32	55	108	1320	30

Frederic C., Case No. 2448, was among the early patients treated with marked and rapid improvement of acidosis. His flushed cheeks, dry tongue, acetone odor gave clinical evidence of a severe acidosis which was borne out by laboratory tests. A summary of his record follows.

TABLE XX

Disappearance of Acidosis and Glycosuria with Insulin and Diet. Case No. 2448.

Date	Diacetic Acid	Sugar in Urine		Alveolar Air	Blood Sugar	Diet				Insulin
						C	P	F	Cals.	
Oct., 1922		%	gms.							units
17	++++	6.9	...	23	....	..	..	..	...	..
17–18	++	6.5	169	..	0.24	110	18	0	512	8
18–19	++	2.4	149	26	....	104	50	28	868	16
19–20	++	2.4	82	26	....	64	29	19	543	12
20–21	++	1.3	42	..	....	36	15	10	294	16
23–24	0	0	...	36	0.20	12	19	24	340	16
30–31	0	0	...	..	0.13	66	49	68	1072	16
Nov. 5- 6	0	0	...	..	..	67	66	106	1486	16

Thomas D., Case No. 1305, entered the hospital on October 20 in typical coma, totally unconscious and unresponsive, with soft eyeballs and Kuss-

maul respiration. Within an hour of his admission, however, his respiration had become shallow and it was evident that prelethal exhaustion was present. His laboratory data were:

TABLE XXI

Diabetic Coma with Death 7½ Hours after Admission.

Case No. 1305.

Date	Urine	Diacetic Acid	Sugar in Urine	Blood Sugar	Plasma CO_2	Insulin
	amt.		%		Vol. %	units
Oct. 20. . .	500 c.c. per catheter	++++	2.8	0.41– 5.30 p.m. 0.53– 8.30 p.m. 0.54–11.00 p.m.	10	8– 5.00 p.m. 16– 8.40 p.m. 16–10.00 p.m.

He grew steadily weaker and died suddenly at 11:50 P. M., October 20. Thomas' symptoms began when he was without insulin for 5 days, and developed a slight infection with fever. Had he returned to the hospital for observation, as advised by a visiting nurse several days before his arrival, insulin might have saved him. But his death in coma does not reflect discredit on insulin, for he was barely alive on his arrival. We cannot believe that any amount of insulin could have been of avail because of the cardiac weakness, but reports from other clinics have been so remarkable that perhaps our supposition is incorrect.

Mr. C., Case No. 2446, carried coal up from the cellar of his home and was feeling fairly well on the morning of December 8. He had a chill at 2 P. M. of that same day and entered the hospital at 8.30 P. M. of December 9. He was drowsy, but not unconscious. Respiration was typically Kussmaul in type and no doubt the depth and noisy character of his breathing helped obscure signs of the true condition of his lungs. During the night the clinical picture changed. Grunting respiration and a cough appeared and respiration became shallow. He died suddenly at 10:50 A. M., December 10. At autopsy lobar pneumonia of the right upper lobe in the stage of gray hepatization was found. The following chart shows improvement in acidosis even in the presence of lobar pneumonia, but no lessening of the hyperglycemia.

TABLE XXII

Relief of Acidosis but not of Hyperglycemia during Lobar Pneumonia

Case No. 2446

Date	Diacetic Acid	Sugar in Urine	Plasma CO	Blood Sugar	Insulin
Dec.		%	Vol. %		units
9.	+++	2.8	20	0.41	. .
9-10.	+	2.8	. .	. . . .	60
10.	. . . . .	. . .	32	0.57	40

The Results of the Omission of Insulin, and Observations Upon the Administration of Insulin by the Mouth

In several portions of this paper mention is made of the case of Thomas D.,[7] Case No. 1305, who in the first part of October, 8 weeks after the beginning of treatment with insulin, omitted it for five days, developed a respiratory infection with fever, resumed a few units, entered the hospital, and died in 7½ hours of coma. (See Table 21.) This boy's diet had been increased 344 calories or 38 per cent. between August 8 and October 4. His death was not entirely due to omission of insulin, but must be attributed in some measure to the increased diet upon which he was living unfortunately temporarily unprotected by insulin. No similar case has developed.

Another opportunity was afforded of learning the effect of the omission of insulin by two attempts to control the diabetes by its administration by mouth.

Miss M., Case No. 1542, our first case, was free from glycosuria on a diet containing carbohydrate, 14 grams; protein, 32 grams; fat, 98 grams. She was receiving 8 units of insulin 2 times daily. This was omitted and a special preparation furnished us through the courtesy of the Eli Lilly Company was administered by mouth. The first day she received 24 units,

TABLE XXIII

Omission of Insulin Subcutaneously and Its Administration by Mouth
Miss M., Case No. 1542

Date	Di-acet-ic Acid	Sugar in Urine	Diet				Total Glucose	Glucose Balance	Blood Sugar	Insulin	
			C	P	F	Cals.				Sub-cutane-ously	By Mouth
		gms.						gms.	%	units	units
Oct.											
23	0	0	14	32	98	1066	43	+43	0.23	16	...
24	0	0	14	32	98	1066	43	+43	....	16	...
25	0	0	14	32	98	1066	43	+43	....	8	24
26	0	12	14	32	98	1066	43	+31	....	0	60
27	0	34	14	32	98	1066	43	+ 9	....	0	84
28	0	36	14	32	98	1066	43	+ 7	....	0	96
29	0	29	14	32	98	1066	43	+14	....	0	96
30	0	33	14	32	98	1066	43	+10	0.29	0	192
31	+	49	14	32	98	1066	43	+ 6	0.25	0	396
Nov.											
1	0	11	14	32	98	1066	43	+32	0.26	16	...
2	0	8	14	32	98	1066	43	+35	....	20	...
3	0	5	14	32	98	1066	43	+38	....	20	...
4	0	0	14	32	98	1066	43	+43	....	..	...

the second day 60 units, the third day 84 units, the fourth day 96 units, and upon the last day 396 units plus concentrated Vitamine B in six doses of ½ gram each. The results are shown in Table 23. During this period the diet remained unchanged. It will be seen that at once sugar appeared in the urine, that it did not increase materially for the first day, but soon rose to 49 grams. Along with the sugar, there was development of slight acidosis. At the end of the period, insulin was begun, and in 4 days the patient had regained her former tolerance. The change in the appearance of the patient during these few days was definite. She resumed the habitus of a severe diabetic—the dry skin, the drawn look, the bright flush in the face, and the decreased brightness of the eye.

Two months later, a similar test of the administration of insulin by mouth was made with Miss Q., Case No. 2687, and, as before, with the full approval of the patient. This test was conducted with a preparation which Professor Clowes of the Eli Lilly Company thought especially desirable for such a purpose. The insulin was given in capsules. The results are to be found in Table 24.

It will be observed that though the patient was essentially free from glycosuria on a liberal diet while taking 26 units of insulin daily, she promptly developed glycosuria, and as in the case of Miss M., this increased irregularly during the period she was receiving the insulin by mouth. As with the former patient, along with the sugar in the urine, acidosis developed.

TABLE XXIV

Withdrawal of Insulin Subcutaneously and Its Substitution by Mouth

Miss Q., Case No. 2687

Date	Diacetic Acid	Sugar in Urine	Diet				Blood Sugar	Alveolar Air	Insulin	
			C	P	F	Cals.			Subcutaneously	By Mouth
		gms.						mm/Hg.	units	units
Dec.										
24-25	+	0	32	55	120	1428	.....	..	26	...
25-26	0	0	32	56	116	1396	.....	..	26	...
26-27	0	2	32	54	116	1388	.....	..	26	...
27-28	0	5	32	56	116	1396	0 20	..	0	68
28-29	0	12	32	55	116	1392	.....	..	0	135
29-30	+++	9	32	55	116	1392	0 19	..	0	270
30-31	+++	30	32	55	116	1392	0 26–6 p.m.	..	0	540
31–Jan. 1	+++	6	32	55	116	1392	0.26–9 a.m.	46	20	210
1- 2	+++	0	32	55	116	1392	.....	..	26	...
2- 3	+++	2	32	55	116	1392	.....	..	26	...
3- 4	+++	10	32	54	116	1388	.....	..	26	...
4- 5	++	6	32	58	116	1404	.....	..	26	...
5- 6	+	4	32	58	116	1404	.....	..	30	...
6- 7	0	0	22	40	48	680	.....	..	30	...
15-16	0	0	31	57	115	1387	.....	..	30	...

H. H., Case No. 1889, was free from glycosuria and acidosis on January 10-11 while taking 10 units of insulin twice a day. The diet was carbohydrate, 81 grams; protein, 64 grams; fat, 109 grams; calories, 50 per kilogram body weight. On the early morning of the eleventh he had an attack of vomiting and developed at 8 o'clock a temperature of 99.5° with no signs of an infection. Gradually during the day he improved. He received no insulin and the diet was reduced to carbohydrate, 36 grams; protein, 14 grams; fat, 30 grams; calories, 460. No sugar was found in the urine in any of the single specimens tested during the day, or in the 24-hour specimen ending the morning of January 12. Having apparently recovered he resumed insulin as before, but although upon his former diet 11 grams of sugar were excreted in the 24 hours, and on the following 2 days, although the carbohydrate was reduced to 62 grams and the total calories made up by increasing the fat, 18 and 19 grams of sugar respectively were excreted. Upon the next day 10 units of insulin were given three times and he became sugar-free. Thereafter the insulin was resumed twice daily without glycosuria and a week later the diet was increased to 71 grams carbohydrate without untoward results.

TABLE XXV

Omission of Insulin During a Gastro-Intestinal Upset
H. H., Case No. 1889

Date	Diacetic Acid	Sugar in Urine	Diet				Blood Sugar	Insulin
			C	P	F	Cals.		
		gms.					%	units
1923—Jan.								
9	0	0	61	64	117	1553	....	20
10	0	0	81	64	109	1561	....	20
11	0	0	36	14	30	460	....	0
12	0	11	81	64	109	1561	0.24	20
13	0	1	62	65	117	1561	....	17
14	0	19	61	64	117	1553	....	20
15	0	0	61	64	117	1553	....	30
16	0	0	62	65	117	1561	....	20

The experience with the cases just cited, who for one reason or another have omitted insulin, is a definite warning of the dangers which a patient will undergo whose diet has been increased with its help. Too much emphasis cannot be laid upon the danger of continuing the high diet when insulin is discarded. The foundations for the diet are certainly removed when insulin is omitted. All patients upon discharge from the hospital should be thoroughly instructed to reduce the diet if for any reason they do not obtain insulin, or if for any reason they suspect the insulin has deteriorated in strength.

Insulin can, however, be discontinued fairly abruptly in at

least three types of patients; (1) those recovering from surgical emergencies; (2) from acute infections, and (3) from severe acidosis in mild diabetes. Rapid changes in insulin dosage may be made under close observation in the hospital, but only gradual changes should be attempted in the home.

The Behavior of Insulin in Infections During the Course of Diabetes.

General Infections. In former years we have always dreaded winters at the hospital because of the development of respiratory infections among the patients and the weeks of treatment lost in consequence. To insulin and the increased diet which it allows must be attributed the more favorable course which such infections take today.

A young man, Case No. 2046, who had had diabetes for 2 years entered the hospital with septicemia, proven by blood culture. The result of the blood culture was not known for the first few days and he was given insulin. Neither good nor harmful effect was noted with the 77 units which he received during the 8 days until it was discontinued. His death from septicemia was unrelated in any way to insulin. A diabetic of many years' duration, Case No. 1931, developed an infection while at home under treatment with insulin. Instead of marked glycosuria he had moderate glycosuria and his diet was not reduced. Colonel P., Case No. 632, withstood an acute respiratory infection while taking insulin far better than on previous occasions and did not need to reduce his diet. There was but a trace of glycosuria. Lloyd H., a young and severe diabetic, developed an infection while becoming sugar-free under dietetic and insulin treatment in the hospital. His diet was not curtailed on account of it and recovery was far more rapid than has been our custom to observe. Miss M., Case No. 1542, our first insulin patient, reentered the hospital with a severe respiratory infection on January 17, 1923. She also recovered with unusual rapidity under undiminished diet and insulin.

The most serious general infection occurred with Case No. 2446, a man of 36 years whose diabetes developed in November, 1921, at the age of 35. He entered the hospital on December 9, 1922, upon the verge of diabetic coma. No evidence of pneumonia was found. He was energetically treated with subcutaneous injections of salt solution, given 80 grams of carbohydrate by mouth and rectum and all the details of treatment for coma carried out. Upon entrance to the Hospital the urine contained 2.8 per cent. of sugar and the acidosis was +++. During fourteen hours in the hospital he received 100 units insulin. The blood sugar increased from 0.41 per cent. to 0.57 per cent. and the CO_2 in the blood rose also from 14 volumes per cent. to 22 volumes per cent. He died 18 hours after admission and an autopsy disclosed a lobar pneumonia in the stage of gray hepatization. (See Table 22.)

The instance of tuberculosis in the diabetic patient Case No. 2148, who also had cirrhosis of the liver has been cited. Insulin was of service at first but, when the tuberculosis became active, was no longer needed, because the tolerance for carbohydrate had risen rapidly up to 76 grams.

Additional evidence that acute infections are better borne with patients treated with than without insulin we believe is afforded by our mortality. Of the 83 diabetic patients treated with insulin since August 7, 1922, 78 are alive today. Of the 5 patients who have died in no instance did this result from an acute infection in a patient who had been receiving insulin prior to its development. One case, No. 705, died of angina pectoris and Case No. 2446 already had advanced pneumonia when he came for treatment. Case No. 1305 died of coma, Case No. 2148 of cirrhosis of the liver and pulmonary tuberculosis and Case No. 2406 of septicemia which was present when he entered the hospital.

Local Infections. Patients with local infections have recovered more quickly with insulin than under the customary, unaided, dietetic and surgical treatment. The case of Mrs. D., Case No. 1245, has already been cited. Case No. 2192 showed distinctly better improvement following his operation for mastoid when insulin was begun. Case No. 2980, Mrs. M., we consider our best case of recovery following amputation from rapidly ascending gangrene. Mrs. M., Case No. 1750, whose diabetes was extremely severe, had a bunion and with R. C. Cochrane's help it healed almost immediately. In former years this might have easily developed into gangrene. Jack K's obstinate and long continued infections of the middle ear and sinuses apparently have been entirely relieved since insulin was begun.

A Diabetic with Relatively High Tolerance for Carbohydrate, but Not for Calories, Gains Calories with Insulin.

During the last few years a small group of diabetic patients have been treated with a diet relatively high in carbohydrate, moderate in protein, and distinctly low in fat. These patients have done well and though adequate time has not elapsed to compare results with cases treated under conditions of low carbohydrate, high protein, and high fat, or of low carbohydrate, low protein, and high fat, our impression is that the high carbohydrate diet is preferable. It is assumed that comparisons between any

of these diets are to be made only when they are faithfully followed by the patients. This subject has been treated with some detail in the Shattuck Lecture for 1922.[8]

One case treated in general along these lines is that of an extraordinarily faithful boy, H. H., Case No. 1889, who developed diabetes in October, 1918, at the age of thirteen years and came under our observation on August 9, 1920. He was then able to take carbohydrate 121 grams, protein 66 grams, fat 61 grams, amounting to 43 calories per kilogram body weight, which was 30 kilograms, 66 pounds. Between that date and reentrance to the hospital on November 9, 1922, his weight fell to 61.5 pounds and his tolerance to carbohydrate 60 grams, protein 45 grams, fat 60 grams, 34 calories per kilogram body weight. Attempts to increase calories by addition of carbohydrate, protein, or fat always resulted in glycosuria. During 64 days of treatment with 860 units of insulin his weight has risen to 72.8 pounds. His diet now is 1553 calories or 46 calories per kilogram body weight. On January 18, 1923, he walked 10 miles, measured by a carefully adjusted pedometer, and perhaps was over-enthusiastic on returning to the hospital when he remarked that he was ready to walk 10 miles more. This boy developed several reactions in the hospital although the carbohydrate in his diet was never below 61 grams when receiving insulin. With his increased diet he had one digestive upset during which 43 grams of sugar appeared in the urine in twenty-four hours.

In sum, these experiences with an intelligent and painstaking patient show that (1) the increase allowed by insulin may be possible only in calories and not as would be theoretically anticipated in carbohydrate; (2) the difficulty of avoiding reactions under even the most favorable conditions; (3) that the advantage of increase in diet may be nullified by an unexpected attack of diarrhea and vomiting.

Insulin in the Home

The million members of the Diabetic Club of America occasionally spend a few days in their various hospital club houses, but for the greater part of the time, like most club members, they live at home. If insulin is to be of permanent help in diabetes, it must be usable by diabetics in their own dwellings. Constantly in the present paper reference has been made to the improvement which patients have obtained after leaving the hospital. In most cases the improvement has been fully as great and in many instances greater than before they were discharged. Our attitude toward the treatment of diabetic patients in general has governed us in this regard and dosage with insulin has been kept low and calories in the diet have been kept low as well, in order that the home treatment of insulin might be safe. In the

second month of treatment Thomas D. died in coma, apparently as a result of having omitted insulin in his home. He felt so much better, had so much confidence in the good that he had received from insulin that he probably believed the omission of it for a few days would be of little consequence. We have not forgotten the lesson which his case teaches. If insulin is to be used in the home, the patients must not only be educated in dietetic treatment but they must be educated in treatment with insulin. For this reason our efforts to teach patients the fundamentals of diabetes have been trebled and a special exercise is given each week on treatment with insulin. This has led to happy results and to results not at first appreciated. The increased attention given to education and to insulin has called forth greater cooperation on the part of the patients, and it is quite evident that the increased cost of treatment due to insulin will be largely offset by decreased cost of medical attendance and the shortening of hospital stay.

One of the best examples of improvement of treatment in the home is Miss Pauline C., Case No. 2422, a school teacher who had become much discouraged with her diet and returned to the hospital for treatment with insulin on November 22, 1922. She then weighed 81¼ pounds and was 47 per cent. under standard weight. The quantity of sugar in the urine amounted to 1.8 per cent., and the acid was one plus. During thirty days of hospital stay with dietetic treatment, supported by a total of 352 units of insulin, glycosuria and acidosis disappeared and she gained 5¼ pounds. On December 16, 1922, the carbohydrate of this patient was 54 grams when levulose was given in 5-gram doses three times daily. This she tolerated and along with the levulose extra calories were given in the form of fat. Upon discharge from the hospital she continued to take levulose made by Mr. Bean in Professor Folin's laboratory. Improvement continued at home and she returned to the hospital for a night's stay on January 19, 1923, showing a gain of 1¾ pounds. Her urine contained no sugar. Case No. 2802, Alice S., with her gain of 25 per cent. in weight is a similar instance, because she, too, made this great improvement far away in a country town.

It is alluring to see patients gain weight, but it is our belief that it is safer to increase the diet so moderately and to give insulin in such conservative doses that dangers from its omission or from complications as a result of diet or the disease will be lessened. The directions which we give patients upon discharge from the hospital at present are as follows:

Information for Diabetic Patients Receiving Insulin

1. Learn qualitative Benedict's test. Secure apparatus for same.

This paper was finished Feb. 1, 1923, and sent on that date to the *Jour. Metabolic Research.*—E. P. J.

2. Secure food scales and understand their use.
3. Learn to summarize the diet at each meal in figures of carbohydrate, protein, and fat.
4. All patients should remain in bed ten consecutive hours out of the twenty-four.
5. Insulin is prepared in solutions of different strengths. Know your dose in units (not in cubic centimeters) and how to measure the amount of solution to give that number of units.
6. Syringe and needle must be boiled each time before using. Cleansing of the skin and the top of the bottle with alcohol is also necessary. Immediately after removing the needle, cleanse it and the syringe with cold water.
7. An insulin reaction may occur 1-2 hours after an injection and may be recognized by the sudden onset of severe hunger, weakness, sweating, trembling, or pallor. The first dose of a new preparation should always be half the last dose of an old.
8. A reaction should be treated by eating an orange or taking the carbohydrate portion of the next meal.
9. At present it is not prudent to use insulin without daily examinations of the urine.
10. If your usual exercise is not obtained, on that day reduce your diet.
11. Arrange for a supply of insulin for two weeks in advance.
12. If your supply of insulin fails
    A. Notify your doctor by telephone or telegraph, and
    B. Reduce the diet one-third.
13. Whenever reporting to your physician or hospital
    (1) Submit in writing:
        A. Weight dressed ..... or naked .....
        B. Record of urine tests
        C. Diet C....., P....., F....., Cals.....
        D. Record of insulin used, preparation number, dose, and time given and
    (2) Bring part of mixed twenty-four hour quantity of urine with record of the amount.

Conclusions

1. The number of patients treated with insulin has been 83. In large measure these were chosen from the severer surviving diabetics cared for by us since 1898. One patient of this number after discharge from the hospital omitted insulin some weeks later in his home while upon an increased diet. He re-entered the hospital in coma and died in 7½ hours. There were no other deaths which could be attributed to insulin and no other deaths from coma occurred in hospital among the 204 patients admitted for diabetes during this period of insulin administration.

2. The average number of units of insulin given to 53 of the

patients for an average period of 63 days was 712, or 11 units a day.

3. The blood sugar at the beginning of treatment averaged 0.24 per cent. and at the end of treatment 0.19 per cent. These figures represent the blood sugar taken fasting.

4. The weight of one of the patients was 50 per cent. below normal standard weight, and the average weight of 53 of the patients was 29 per cent. below standard weight.

5. The greatest gain in weight was 9.7 kilograms, and the average gain 2.6 kilograms. The greatest percentage gain in weight was 25 per cent., and the average 7.6 per cent.

6. The total calories given the patients rose from 26 to 38 calories per kilogram body weight. The carbohydrate rose from 37 grams to 45 grams, the protein from 36 grams, or 1 gram per kilogram body weight, to 55 grams, or 1.4 grams per kilogram body weight, and the fat from 62 grams to 105 grams. The ketogenic antiketogenic ratio changed from 1.1 to 1.2.

7. Patients at all ages from 2 years to 77 years responded equally well to treatment, but the youngest cases show the greatest gain in weight. The average number of days for the gain of 1 pound in weight for the different decades of life varied from 7 to 15 days quite irrespective of sequence of decades.

8. Cases of short and long duration also responded equally well to treatment. The average number of days for the gain of 1 pound in weight, according to the years of duration varied from 8 to 19 days, and was also irrespective of the years of duration of the disease.

9. The greatest number of units given anyone in 24 hours was 100. There were but 3 cases who regularly received over 30 units.

10. There is no evidence at present that the dosage must be increased if we disregard the increase at the beginning of treatment, which corresponds to the constantly increasing diet, and also take cognizance of the undernutrition of the patients.

11. A total of 30 reactions have occurred in 11 of the 83 patients during the administration of 5153 doses of insulin. A reaction developed following the injection of 1 unit of insulin with a man who had a tolerance for 114 grams of carbohydrate but was weakened by diarrhea. During the reactions the blood sugar at no time fell below 0.03 per cent. All reactions occurred between a quarter of an hour and three and three-quarters hours following injection of insulin.

12. The importance of diarrhea in rendering patients liable to hypoglycemic reactions is suggested.

13. The basal metabolism increased 9 per cent. in a series of 11 patients. In one case it rose from —43 per cent. to —22 per cent. during the course of treatment and in another from —24 per cent. to —5 per cent.

The respiratory quotient rose with food after insulin to above unity.

14. General infections were uninfluenced by insulin, save that complicating acidosis was lowered. Local infections appeared to heal more rapidly.

15. The omission of insulin resulted in the reappearance of glycosuria which did not reach its height until the fifth and last day of the omission of the drug.

16. The administration of insulin by the mouth in two cases was without effect.

17. A diabetic with relatively high tolerance for carbohydrate, but not for calories, through insulin increased his caloric tolerance but not his carbohydrate tolerance.

18. Patients treated in the hospital with insulin continued successfully the treatment at home, due to additional training in diet as well as in insulin medication.

19. Information for diabetic patients receiving insulin is recorded.

20. The use of insulin involves grave responsibility for physicians. Painstaking education of the patients and close observation at frequent intervals will protect both patient and doctor.

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CLINICAL OBSERVATIONS ON INSULIN

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We are submitting herewith in the nature of a preliminary report a summary of observations with a preparation of insulin*, supplied by Eli Lilly and Company of Indianapolis through the courtesy of the insulin committee of the University of Toronto.† We have now treated forty‡ cases of diabetes with insulin and are glad to be able to confirm in all essential particulars the strik ingly beneficial therapeutic action of insulin reported from the the University of Toronto. For discussion here those phases of the subject have been selected which we may be able to clarify by presenting definite data.

A Method of Clinical Assay

It was recognized early that there were discrepancies between the strength of insulin as determined by its effect on rabbits, and its action on the glycosuria of the diabetic patient. The rabbit test developed by the investigators of the University of Toronto has thus far been the method of assay. One unit of insulin is one-third amount necessary to cause convulsions by hypoglycemia in a rabbit weighing 2 kg. An explanation of the discrepancies noted may be deterioration subsequent to the preliminary rabbit testing. This is still a question, and can only be settled by repeated assay of material, both on the rabbit and on the diabetic patient. For this purpose, as well as for the purpose of controlling the routine treatment of patients, it is desirable to have some manner of expressing the potency of the material in

* The word "insulin" is used in the text to indicate the active principle of the pancreas, and the word "iletin" for the commercial preparation manufactured by Eli Lilly and Company.

† A very convenient summary of their studies on insulin, thus far reported, is contained in this Journal, 1922, ii, 125-140.

‡ Since this paper was submitted for publication, February 1, 1923, we have treated 200 patients. The results with these patients substantially confirm the observations made on the preliminary group.

units that will be referable to grams of sugar made available to the patient. It would seem desirable, therefore, to devise and formulate a method of clinical assay which would permit the translation of the rabbit unit into terms expressing the number of grams of glucose which the unit may be expected to metabolize. Ultimately, it should be desirable to adopt some such glucose standard for general use.

After preliminary trials we have adopted the following routine method of testing each new lot of insulin received. A hospital service of between forty and fifty patients with diabetes has made it possible to select for the test, patients who are free from infections or other complications, and who are faithful in carrying out directions and comparatively calm in temperament. The tolerance for glucose is determined under standard dietetic conditions and without insulin, then a dosage of insulin (20 to 40 iletin units) is chosen, the daily administration of which will permit an increase of the diet to a standard food mixture of about 2500 calories. The tolerance on this higher regime with insulin minus the original or basal tolerance gives the grams of glucose the utilization of which is attributable to insulin, and this, divided by the number of units employed, the glucose value of each unit.

The standard preliminary diet is the basal maintenance food mixture discussed in a previous publication.[14] It consists of calories sufficient for basal maintenance, 0.67 gm. of protein for each kilogram of the patient's body weight, low carbohydrate and higher fat. The two latter food elements are adjusted[14] in such a manner that the proportion between ketogenic molecules and antiketogenic glucose molecules is safely within an aketogenic ratio. So far as is practicable, foods are chosen whose composition can be reckoned from food tables with reasonable accuracy. In order to carry out the test, an estimable amount of sugar should remain in the urine; therefore, whenever necessary, a definite addition of carbohydrate is made to the diet, so that from 5 to 10 gm. of sugar is excreted daily with constancy. In order to minimize errors in the diet kitchen and in the excretion and collection of urine, averages of several days are used in re-calculating the diet and in estimating the excretions of nitrogen and glucose.

The glucose value of the food for metabolism is calculated from the urinary nitrogen and the fat and carbohydrate of the

diet. The ingested protein is disregarded and sugar from protein sources is determined by multiplying the number of grams of nitrogen in the urine by the factor 3.7. The glycerin fraction of the fat is considered to be sugar, in accordance with Woodyatt's assumption,[17] and therefore one-tenth by weight of the fat is calculated as glucose. The consistency of results obtained in these assays may be regarded as evidence in favor of this assumption. The carbohydrate of the diet is calculated as so much glucose.

The basal tolerance is the difference between the glucose value of the standard food mixtures and the average daily glucose excretion. After this has been determined, a higher diet and a dosage of insulin are designed so as to strike a level just above the new glucose tolerance anticipated as a result of the insulin. As a rule, one rabbit unit of iletin assays between 1.5 and 2 gm. of glucose. The rule, therefore, is to add to the glucose value of the diet 2 gm. of glucose for each unit of iletin. The protein allowance is maintained practically the same as before between 0.67 and 1 gm. for each kilogram; the fat is readjusted so as to give the maximal number of calories which the higher glucose figure will permit and still maintain the safe aketogenic-ketogenic ratio. This calculation is simplified by a nomographic chart.[14]

The diet and the higher dosage of insulin are continued for several days. Both sugar and nitrogen excretion usually become reasonably uniform within a day or two. The nitrogen output is then averaged, and the glucose value of the food metabolizing recalculated. The average glucose excretion substracted from the glucose in the high diet in excess of the original or basal tolerance gives the number of grams of glucose accounted for by the iletin administered.

Illustrative Procedure

Case 1 (A409678), Table 1, basal glucose tolerance 47.3 gm. In this case an iletin dosage for twenty-four hours, 16 units was selected. The value of this was assumed to be 2 gm. for each unit, which should permit a glucose limit of the basal tolerance 47.3 gm. plus 32 gm. resulting from the insulin, or 79.3 gm. The body weight was 52.5 kg. which permitted, according to the rule, a protein intake of 35 gm. As reasonably close nitrogen equilibrium was anticipated, it was estimated that 58 per cent. of this 35 gm. or 20.3 gm. would represent the amount of glucose derivable from the protein metabolism. Subtracting this from the glucose limit of 79.3 gm. left 59.0 gm. of glucose permissible from fat and

carbohydrate sources. The point equivalent to 35 gm. was located on the protein scale of the nomographic chart. A ruler pivoting on a needle inserted at this point was moved up on the horizontal parallel fat and carbohydrate scales until the addition of one-tenth of the fat number to the carbohydrate number equalled 59.3. The ruler in this position indicates the composition of the diet as well as the total number of calories, namely, protein 35, fat 190, carbohydrate 35, calories 2054.

The glucose value of the higher food mixture was 80.6 gm., from carbohydrate 35, from fat 19, from protein as estimated from the actual excretion of nitrogen 26.6. The basal tolerance was 47.3, leaving glucose in excess of basal tolerance 80.6 minus 47.3, or 33.3. The average glucose excretion was a faint trace and was disregarded. Thirty-three and three-tenths grams glucose being accounted for by the 16 units of iletin employed, the clinical assay, $\frac{\text{glucose}}{\text{units iletin}}$ was $\frac{33.3}{16}$ or 2.1.

It is important that at least a definite trace of sugar remain in the urine, 5 gm. or more in the twenty-four hour specimen; other-

TABLE I

C.E.B. Clinical Assay of Insulin

Case A409678, a man, aged forty-six years. Duration of Diabetes two years, six months.

	Period, days	Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories	Nitrogen in urine, gm.	Dextrose in food metabolized, gm.	Dextrose in urine, gm.	Tolerance dextrose, gm.	Increase in tolerance from iletin, gm.	Iletin dose, units	Assay dextrose for each unit of iletin, gm.
Tolerance test (no iletin)	4	35	138	22	1517	7.3	62.8	15.5	47.3			
Iletin 724225	3	35	190	35	2054	7.2	80.6	Faint trace		33.3	16	2.1
Iletin 725338	4	35	190	35	2054	6.4	77.7	Faint trace		30.4	20	1.5
Iletin 724828	6	35	190	45	2095	6.9	89.5	Faint trace		42.2	16	2.6
Iletin 725682	6	35	190	47	2103	5.8	87.46	0		40.16	20	2.0

wise no conclusion can be drawn regarding the maximum strength of the iletin. If enough iletin were given to cause a complete disappearance of sugar some must go to waste, so to speak, at least an incomplete record of its effect would be obtained.

Since many variables enter into these calculations, they must be emphasized. Strict adherence to standard low protein diets and the enforced rest in bed during the estimate of the basal

tolerance increases the reliability of the results, as does also the averaging of the diets and urinary excretions for periods of several days. Considerable errors, however, are difficult to avoid. It is obviously impossible to subject the number of patients involved to the rigors of perfect metabolism experiments; in consequence, ward measures of feeding and urine collection have been depended upon. The greatest source of error is a fluctuation of the basal tolerance, either an improvement or a depression. Depressions are not likely, apparently, unless recognizable complicating infection intervenes. We have as yet seen no evidence of a fall of basal tolerance in these patients. On the other hand, there have been a few in whom we thought we could see a noticeable increase in tolerance. One patient, in particular (Case 2, A402666, a man aged twenty-eight years, with uncomplicated diabetes of acute onset in February, 1922) seemed to give fairly definite evidence of such improvement. The patient was admitted to the hospital in August with severe symptoms. October 2, after control of the acidosis, but before insulin was used, the basal tolerance was 84 gm. November 30, during a period without insulin, it was 79 gm., that is, approximately the same as before. December 14, the tolerance calculated during a period when he was receiving 15 units of iletin 725338, was 145 gm. This lot of iletin assayed on the average 1.6 gm. of glucose for each unit, in other cases. Subtracting from 145 the number of grams of glucose attributable to this iletin, leaves a basal tolerance of 121, an increase over the original or basal tolerance of 37 gm.

While the method of assay described is crude in the respects noted, the results of assays of the same lots of iletin made on groups of patients have been fairly consistent. This is illustrated in Table 2. The method may, therefore, have a definite usefulness so long as we are dependent on insulin preparations of varying potencies. The procedure is practical in institutions in which a sufficiently large number of patients are available.*

Subcutaneous Injections, Dosage

Thus far we have given iletin only by subcutaneous injections,

* Since Table 2 was constructed and the data herein reported were submitted for publication, the uniformity of various allotments of iletin received from Eli Lilly and Company has improved very considerably. The table covers the experimental period only, when methods of manufacture were being developed, and since the conclusion of that period preparations that we have been receiving have been of very standard potency, the unitage exhibited by different lots being constant within the limits commonly set for biologically tested preparations.

TABLE II

Summary: Clinical Assay of Insulin

Iletin* number	Case	Dextrose equivalent per unit	Average assay
722840	A409769	1.6	1.6
722838	A409769	0.9	0.9
724212	A409769	0.5	0.5
724225	A409769	2.5	
	A409678	2.1	2.3
724837	A411429	1.0	1.0
725338	A409678	1.5	
	A411514	1.1	
	A410516	2.1	1.6
725676	A411429	1.4	1.4
724828	A409678	2.6	
	A330175	2.0	
	A411514	2.7	
	A410516	3.1	
	A363756	2.8	
	A411429	2.3	2.6
725682	A409678	2.0	
	A411514	1.9	
	A410516	1.9	
	A363756	1.9	
	A411429	1.4	1.8
725683	A411514	1.4	
	A409769	1.9	1.7
725695	A330175	1.2	1.2
725699	A410516	1.3	
	A363756	1.1	1.2
725679	A411514	1.4	
	A411429	1.4	1.4
725703	A330175	1.3	
	A411429	1.5	1.4
725704	A330175	0.9	
	A410516	1.1	
	A411514	1.3	
	A363756	1.2	1.1
725707	A411514	1.9	
	A363756	1.7	
	A411429	1.8	1.7
725708	A330175	1.2	
	A412711	1.2	1.2
725710	A414106	1.2	
	A341632	1.8	
	A330175	1.2	
	A412711	1.7	
	A329800	1.4	
	A382508	1.6	1.5
725733	A330175	1.3	
	A414460	1.1	
	A329800	1.3	
	A382508	1.4	1.3
Average		1.59	1.45

*Eli Lilly and Company. See footnote ( ).

chiefly into the loose aureolar tissue of the arm, side, or buttocks. Slight pain at the site of injection often occurs and may be followed during the next twelve hours by moderate induration of the part with some heat and throbbing. This is particularly true when more dilute preparations are used, necessitating bulky injection of 5 c.c. or more. With smaller volumes of concentrated preparations there has been practically no subsequent pain or inflammation. When repeated injections are made into one site, an induration of the part occasionally results. Such induration is painless and usually harmless, although severe injury consisting of necrosis and sloughing of the skin occurred in a few instances. Usually the area of skin involved was not more than 10 mm. in diameter, a small, punched-out ulcer resulting, which healed rather tardily. One patient, a child (Case 3, A385906), developed a necrotic area 10 by 4 cm. on the thigh, probably an unsuitable site for the injection because of the tightness of the tissue. The area became a deep, painless ulcer with sharply demarcated edges extending down to the muscle but not involving it. Despite careful dressing eight weeks were required for healing. Dermatological consultants believed that these areas of necrosis and ulceration were attributable to the preservative (tricresol) contained in the preparation. The areas had the appearance of and behaved like the necrosis following phenol burns. There was no evidence of infection, and it is quite probable that the explanation offered by the dermatologists is correct, particularly since all the trouble encountered was with the more dilute preparations, requiring relatively bulky injections. It is possible that the necrosis in these cases resulted from material entering the epidermis, although great care has been exercised to avoid catching the point of the needle in the skin.

The size of the dose in iletin units depends on the basal tolerance of the patient, and on the diet. In general, we aim to provide a food allowance of about 2000 to 2600 calories. The glucose tolerance of the fairly severe and the severe cases of the acute type of diabetes of two or more years' duration, when determined on the basal maintenance diet (page 703), is usually between 20 and 70. Since the average glucose value of an iletin unit is from 1.5 to 2 gm., between 10 and 30 iletin units are required to raise the tolerance sufficiently to permit this desired higher caloric diet. With preparations of average strength, 30 units is the maximal dose. The adjustment of the

diet to allow the greatest number of calories for a limited glucose allowance has been described in a previous publication.[14]

Maximal results seem to be obtained from a given daily dose of insulin with a single injection of the entire amount about thirty minutes before breakfast and with food distributed equally between breakfast at 8:00 a.m., dinner at noon, and supper at 5:30 p.m. This conclusion has been reached as the result of observations, such as the following:

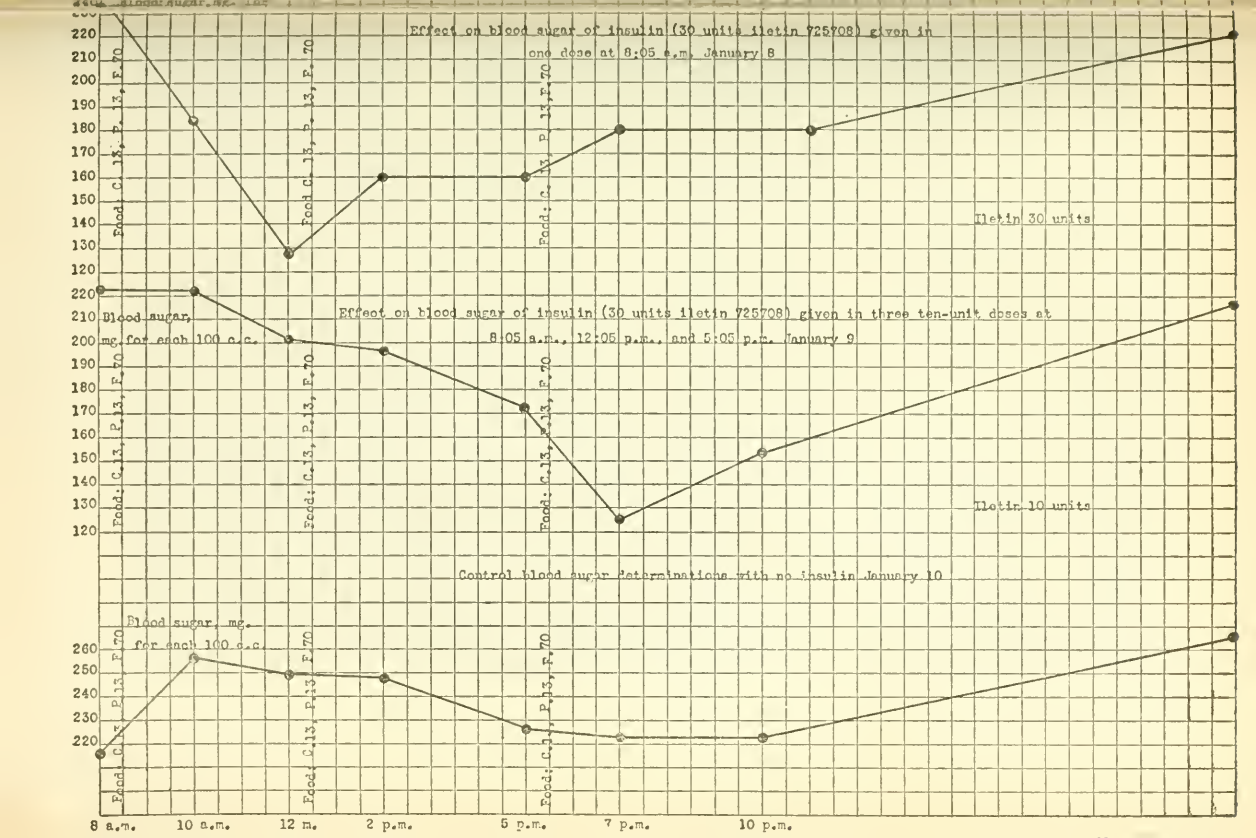
The patient in Case 2 receiving 15 units of Iletin 722845 in each single morning dose, excreted traces and faint traces of glucose not to exceed 5 gm. a day from December 3 to 9, 1922. He was then given the same lot of iletin in 5 unit doses repeated at 6:15 a.m., 10.30 a.m., and 4:00 p.m. The urine did not change for the next two days. Stronger iletin, Iletin 725338 was then substituted and accompanied by an increased glucose allowance of 20 gm. This was continued for two days in three divided doses, each of 5 units, with slight traces only of glucose in the urine. December 14, with the same iletin and the same diet, the 15 units were given in one dose. The same or slighter traces of sugar were found in the urine the following three days. No symptoms of hypoglycemia were noted.

December 5, 1922, a girl aged thirteen years (Case 4, A410516) was receiving 20 units of Iletin 724225, in two doses, one-third at breakfast, and two-thirds at noon. The food was equally divided between the three meals. The case was just balanced, a very faint trace of sugar appearing irregularly in the urine. Symptoms of mild hypoglycemic reaction occurred December 5 and 6. December 7 and thereafter, the entire dose was given at once before breakfast without subsequent glycosuria or reaction.

November 23, 1922, a boy aged two years (Case 5, A386254) who had been receiving two injections of 5 units each of Iletin 722838 was given a single 8 unit morning injection of the same preparation without alteration in the urine.

Serial examinations of the blood sugar level after single and multiple injections of iletin also suggest that a single morning injection of a given amount will produce as great an average reduction of the blood sugar level as can be accomplished by dividing the dosage, when average sized doses of insulin are used.

The data of such an experiment are presented in Chart 1. The observation was made on a man aged twenty years (Case 6, A411514) who had had severe diabetes for more than two years and whose basal tolerance was 29. He was just sugar free with 30 units of Iletin 725704 and a diet containing carbohydrate 40 gm., protein 35 gm., and fat 210 gm., divided into three equal meals. He had been on this regime for the preceding four days, the iletin being given in one dose at breakfast. The experiment covered three days. Curve A shows the behavior of the blood sugar on January 8, 1923, with insulin (iletin 30 units) in one


Effect on blood sugar of insulin (30 units iletin 725708) given in one dose at 8:05 a.m. January 8
Iletin 30 units
Blood sugar, mg. for each 100 c.c.
Effect on blood sugar of insulin (30 units iletin 725708) given in three ten-unit doses at 8:05 a.m., 12:05 p.m., and 5:05 p.m. January 9
Iletin 10 units
Control blood sugar determinations with no insulin January 10
Blood sugar, mg. for each 100 c.c.
Food: C.13, P.13, F.70
8 a.m.
10 a.m.
12 m.
2 p.m.
5 p.m.
7 p.m.
10 p.m.

dose immediately before the morning meal. It will be seen that the maximal depression occurred shortly before the noon meal. Curve B is drawn from data obtained January 9, and is a continuation of Curve A. On this day 30 units of the same preparation were administered in three doses, 10 units before each meal. The maximal depression with this divided dose was not reached until late afternoon. The effect on the blood sugar level for the balance of the twenty-four hours was practically the same after the divided dose as with the single morning dose. Curve C is a continuation of Curve B and was obtained during the following twenty-four hours without iletin. It is probable that Curve C was markedly influenced by the effect of the iletin of the preceding days and was considerably flatter than it would otherwise have been. This experiment is not entirely satisfactory and the matter is being studied further.

The question whether a single large morning injection is attended with greater danger of hypoglycemia can be answered, we believe, in the negative for adults where the dose is not larger than 30 iletin units. The patient in Case 4 is a witness to this. Mild reactions were noted with divided doses of insulin (Iletin 724225) November 5 and 6, 1922, and were absent when the same amount of the same material was administered in one dose daily, between November 6 and 9. Blood sugar data, such as that presented in Charts 1 and 2, reveal a lag between the injection of insulin and the period of its maximal effect. This delay may amount to several hours and will depend on the amount of food ingested. Often, if the injection is made in the morning, the second meal may be early enough to neutralize any severe effect on the glycemic level. In any case, the danger of a hypoglycemic reaction can be minimized by balancing the diet carefully, and if symptoms should arise by prompt administration of small amounts of sugar. The practical advantages of the single administration are so obvious as to require no comment.

Until now, it has seemed desirable to insure against hypoglycemia by so balancing the diet and the insulin dosage that the twenty-four hour urine collections would show a trace of sugar persistently. This mild glycosuria and the accompanying hyperglycemia have been regarded as a buffer. It may be unnecessary and even harmful to provide this insurance, but so far as we have been able to observe, the improvement of the patient has continued uninterruptedly in spite of it. Indeed, the patient in Case 2, as has been noted, gave evidence of actual improvement of basal tolerance despite the fact that for three months there was a glycosuria of from traces to 76 gm. daily. The larger

excretions occurred during a period of special investigation without insulin.

Insulin Reactions

We have observed two types of reactions. One, apparently, is a protein effect; the second results from the hypoglycemia provoked from overdosage. The first comes on within a few minutes of the time of injection and is not accompanied by a fall of blood sugar level; the second is delayed for at least two hours after the injection. Since certain symptoms are common to both reactions, it is possible, unless the blood is examined, to mistake the one for the other. The protein reaction has been observed in only three patients and only with earlier preparations. It has not occurred with the purified products received recently.

The patient in Case 2 had been without insulin for five days, and received, December 2, 1922, at 8:10 a. m., 30 units of Iletin 722845, followed by a light breakfast. At 8:15 a. m. he was nauseated, his face flushed, and he vomited. Severe pain developed in the epigastrium followed by diarrhea and profuse sweating. The pulse, at first full and bounding, became weak and slow, 50 each minute. At 8:50 a. m. he was drowsy, the epigastric pain was less severe, but persisted as a dull ache. One hundred grams of orange juice were given by mouth. At 9:00 a. m., he was more alert and by 9:10 a. m. all the symptoms had disappeared and the pulse was strong, with a rate of 86 each minute. This reaction was believed to be due to hypoglycemia, particularly because the symptoms abated so promptly after the orange juice was given. We were disillusioned, however, as soon as the report of the blood sugar reached us. Blood drawn at 8.45 a. m. contained 270 mg. of sugar for each 100 c.c. At 10:00 a. m. a moderate urticarial rash developed around the arm and, to some extent, on the face, supporting the evidence that the reaction was not due to hypoglycemia, but was a protein effect.

The patient in Case 5 had an urticarial rash December 7, the third day on which Iletin 724212 was given. He had previously tolerated Iletin 721941, 722840, and 722838. The day following the reaction, he was given Iletin 724828, which he tolerated and no further trouble was experienced.

Case 7 (A382444), a girl aged two years, received iletin in inadequate doses, but without reaction from September 23 to October 1, 1922. A period of five days followed without injections. Iletin 5000 was then started and on the third day, October 8, a profuse urticaria broke out over the entire body, persisting throughout the day and further aggravated by a small dose the next day. Iletin was discontinued for the time, but a week later, October 18, 0.5 c.c. of Iletin 5025 produced a still more severe reaction. A generalized red blush appeared over the body five minutes after the injection. This was accompanied by reddening of the eyes and puffing of the face. The respiration became labored and the pulse rapid. The red blush soon gave place to an itching papular rash. The entire picture was so alarming to the parents that they took

the child from the hospital. When last heard from the child was being treated by a well-known therapeutist in the far West whose methods, while they may be of doubtful value in some respects, are at least less alarming.

Slight reactions due to hypoglycemia have been noted with a few patients, but only occasionally. They have consisted merely of weakness and a sense of anxiety, a sense of trembling, and occasionally, a feeling of hunger. When the reactions occurred between meals, 100 gm. of orange juice was administered, and controlled the condition.

Severe reactions were observed in the small child in Case 5 who received 12 units of Iletin 722838 for two days and then the same dosage of Iletin 724212 for three days, without symptoms other than the protein effect described. The urine contained a trace of sugar each day. The diet consisted of carbohydrate 26 gm., protein 35 gm., and fat 70 gm., divided equally in three meals. Iletin 724225, a strong preparation, as shown by the assay summary, was then substituted. On the first day all went well, although the trace of sugar disappeared from the urine. Four units were given in the morning, and eight at noon. On the second day, with the same dose, of the same lot, given in divided doses as before, the child roused from his nap at 3:00 p.m., and began pulling at his hair. Soon thereafter he relaxed completely with wide, staring eyes and internal strabismus. A few minutes later he was in coma so deep that corneal reflexes could not be elicited. At this time 100 c.c. of orange juice was given by mouth. The first mouthful was taken with difficulty. A few seconds later swallowing was easier. Within five minutes by the clock, complete consciousness had returned and the child was out of bed and playing with his toys. No further carbohydrate was needed. Unfortunately, no blood sugar determination was made. The following day at 7:30 a.m., the child received 12 units of the same strong iletin. The diet and its distribution between the three meals remained unchanged. At 9:20 a.m., a complaint of hunger and sleepiness was heard. The child then closed his eyes and started to sleep. The muscles were flaccid, the pulse 128. Blood drawn at 9:30 a.m., contained 37 mg. of sugar for each 100 c.c. One hundred grams of orange juice was given by mouth. Almost immediate improvement was noted and within seven minutes there was no more word of sleep and the child was actively at play.

This case emphasizes both the seriousness of these hypoglycemic reactions and the specificity and reliability of the antidote. The first reaction, coming during the child's nap, might well have escaped attention. The events described may be an additional argument in favor of the single large dose in the morning. The reaction which such morning injections may provoke, will occur during the morning hours when patients are least likely to be napping, and not later in the day, as happened

here with the divided dose. The remarkably rapid response to a very small amount of orange juice, representing no more than 10 gm. of carbohydrate, is of interest. A similarly rapid effect of glucose, given intravenously, has been noted by Mann in dogs with convulsions from hypoglycemia, following removal of the liver. It would seem that the mere presence of a sufficient concentration of glucose molecules in the blood is essential to life. Curiously enough, fructose injected into Mann's hypoglycemic dogs does not restore them; yet, fructose, chemically, is more reactive than glucose.

The reactions described illustrate the very serious dangers that accompany the introduction of this new treatment of diabetes, and justify the control of the manufacture and distribution of insulin which has been instituted by the University of Toronto. The reactions emphasize, furthermore, the importance of expert and watchful management by the physician who is permitted to use insulin in the treatment of such patients. It is obviously of vital importance to limit the distribution of insulin to specially organized diabetic clinics, and to physicians who have had some special training in this field until the profession in general has become better advised with regard to the dietetic technic necessitated by this method of treatment, and until a more accurate method for the standardization of preparations of insulin has become available.

Indications for the Use of Insulin

Until a more liberal supply becomes available, it would seem unjustifiable to employ insulin in the earlier stages of the acute type of the disease, or in the chronic, nonprogressive forms in which dietary control alone should suffice to hold the patient in a fair state of health. With very few exceptions, therefore, we have reserved our allotment for the severe cases. It seemed desirable, for experimental purposes, to start the treatment on one very early case of diabetes of the juvenile acute type, to see whether results could be obtained that might be called curative. We have also given insulin to two patients with mild diabetes and arteriosclerosis who were losing weight and strength, and declining rapidly. Both are subjectively improved and are gaining a very little in weight. Postoperative acidosis attributable to anesthesia or to the shock of an operation can be successfully prevented in nearly all, except emergency cases, by preoperative

dietetic treatment, skillful operative technic and judicious postoperative management. Nevertheless, this is a field in which insulin will at times prove a great aid. In the treatment of other surgical complications, particularly serious infections, it will also be of great usefulness. The following brief report of a chronic case of diabetes, complicated by empyema, illustrates this.

A man, aged forty-six years (Case 8, A410834) with chronic empyema since April, 1922, drained five months after onset, came to the Mayo Clinic November 19, with reaccumulated pus in the chest. Glycosuria had first been noted in July. The patient had lost 80 pounds in weight. The urine contained 2 per cent. sugar but not more than 20 gm. each day on a qualitative restriction of the diet. The blood sugar was at times as high as 350 mg. for each 100 c. c. Exploration of the chest and open drainage were performed November 24, and December 7. December 9 the general condition was bad; the pulse was 100, and hyperglycemia and glycosuria persisted despite dietary measures. The surgeons believed that prospects of recovery were poor unless the diet could be raised. Insulin in doses of 15 iletin units daily was started December 9 and was continued without interruption until January 15, 1923. The urine cleared promptly and the diet was increased to 1900 calories, then to 2100 calories, and finally to 2400 calories. A steady improvement resulted. The gain in weight has been marked and continuous. The cavity of the chest diminished in four weeks from a capacity of 960 c. c. December 7 to a capacity of 45 c. c. January 5. A thoracoplasty will soon be made.

Acute acidosis, either in the severe or chronic cases, is unquestionably an indication for insulin. The dramatic results reported from the University of Toronto have been repeatedly observed in such cases. Two patients (Case 9, A411219, and Case 10, A409679) both with plasma carbon dioxid combining power of 18 volumes per cent., one with a blood fat of 9 per cent., were restored to symptomless conditions and normal acid base equilibrium within thirty-six hours. One patient received a total of 50 iletin units in three doses, and the other, 60 units. Each had 600 gm. of orange juice. No alkalis or other drugs were employed. We have not found it necessary to accompany the doses of insulin in these cases with other than small doses of carbohydrate, and we do not believe it advisable to resort to larger doses of sugar intravenously or otherwise. The tissues of these acidotic patients are saturated with sugar and considerable quantities of insulin should be tolerated without danger of hypoglycemia. Adding sugar should merely delay results.

Special Studies in Metabolism

In Tables 3, 4 and 5 will be found summaries of the more essen-

TABLE 3

Summary of Metabolism Experiment 1

Case 11, A210411, J.C.B., a man aged forty-four years, height 177 cm..

Period	Days in period	Iletin dose, units	Weight, kg.	Food				Basal metabolism			Urine						Blood				
				Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories	Respiratory quotient	Calories, twenty-four hours	Rate, per cent	Volume output, c.c.	Nitrogen in urine, gm.	Nitrogen balance*, gm.	Sugar, gm.	Creatinin, gm.	Diacetic acid, scale 1 to 4	Sugar, gm.	Plasma, carbon dioxid, per cent	Acetone, 150 c.c. for each	Fat, per cent	
I	2	0	59.5	79	175	172	2651	0.86	1414	-11	3833	9.33	+2.05	66.5	1.37			60.8	0	1.11	
II	1	2	58.8	79	175	172	2651	0.85	1457	- 8	3220	9.58	+1.80	59.8	1.48	0	0.33	56.9	0	1.04	
III	3	5	58.3	79	161	172	2518	0.81	1354	-14	2660	9.85	+1.53	71.3	1.76	0	0.33	57.8	0	1.19	
IV	2	10	59.6	79	175	173	2653	0.87	1401	-12	1620	8.69	+2.69	39.3	1.39	0	0.34				
V	1	0	60.5	79	175	174	2661	0.92	1529	- 5	3250	9.55	+1.83	72.2	1.56	0					
VI	1	5	60.5	79	175	174	2661	0.95	1526	- 5	2665	8.19	+3.19	64.1	1.61	0					
VII	1	0	62.2	79	204	174	2934	1.02	1593	- 2	2250	6.07	+5.31	41.3	1.25	0	0.29				
VIII	3	15	62.4	79	160	174	2521	0.78	1457	-10	3328	7.08	+4.30	47.9	1.55	0					
IX	2	0	60.8	79	157	172	2483	0.80	1403	-13	2865	7.80	+3.59	73.8	1.38	0	0.27	56.5	0	1.0	
X	2	30 1 day 20 1 day	61.6	79	167	172	2578	0.81	1455	-10	2518	5.78	+5.61	16.0	1.11	0					
XI	1	0	62.2	79	175	172	2651	0.80	1534	- 6	2230	4.03	+7.35	82.3	0.79	0	0.31	61.2	0	1.05	

* Nitrogen balance determinod by adding 10 per cent of food nitrogen to urine nitrogen to obtain excreta nitrogen

tial part of the data obtained in three cases of diabetes (Cases 11, 2 and 12) during periods of detailed and carefully controlled metabolic study. The laboratory method and the technic of the investigation were essentially the same as those described in a report of a similar nature from this Clinic.[15] The only deviation of importance was a daily analysis for fat of the milk and cream used, which permitted a more accurate calculation of the composition of the diets. The charts record data, grouped into periods, such as the weight, the basal respiratory quotient, the basal calories for twenty-four hours, the basal metabolic rate, the calculated composition of the diet in grams of protein, fat, and carbohydrate, and its total calories, the daily urine volume, the daily urine nitrogen excretion, the nitrogen balance, the daily urine dextrose excretion, the daily urine creatinin excretion and qualitative diacetic acid reaction. Intermittent observations of blood sugar values, plasma carbon dioxid combining power, blood fat, blood acetone bodies, and in one case, amino-acids are included. The respiratory quotients and basal metabolic rates were obtained by the gasometer method of indirect calorimetry, according to the regular routine adopted in the metabolism laboratory at the Clinic, and described in detail by Boothby and Sandiford. The blood for analysis was taken before breakfast. Brief abstracts are given of these three cases containing the essential details of their clinical records previous to the admission of the patients to the metabolism ward:

A man (Case 11, A210411) aged forty-five years, was examined in the Clinic February 20, 1922. He had had an acute onset of diabetic symptoms in May; no attempt had been made at dietary control. Appendectomy had been performed in 1907 and gastro-enterostomy in February, 1922 because of symptoms of gastric ulcer since 1905. At that examination a trace of sugar was found in the urine. The weight was 160 pounds. The patient was admitted to the hospital July 22; he then weighed 137 pounds. There was a maximum of 75 gm. glucose in the urine the following three days on an observation diet containing carbohydrate 150 gm., protein 60 gm., and fat 60 gm. The Gerhardt test of the urine was positive and the blood sugar was 263 mg. for each 100 c.c. Acidosis and glycosuria were controlled by dietary adjustment. The patient was transferred to the metabolism ward for special study August 24.

A man aged twenty-eight years (Case 2) had an acute onset of diabetic symptoms with inadequate dietary control February, 1922. There was no history of infection. The weight previous to the onset of diabetes was 140 pounds. The patient was admitted to the hospital August 24, weighing 111 pounds. There was a maximum of 60 gm. glucose in the daily urine of the following three days on an intake of 600 gm. of orange

TABLE 4

Summary of Metabolism Experiment 2.

Case 2, A402666, M.A., a man aged twenty-eight years, height 171 cm.

Period	Days in period	Rietin dose, units	Weight, kg.	Food				Basal metabolism			Urine						Blood			
				Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories	Respiratory quotient	Calories, twenty-four hours	Rate, per cent	Volume output, c.c.	Nitrogen in urine, gm.	Nitrogen balance*, gm.	Sugar, gm.	Creatinin, gm.	Diacetic acid, scale 1 to 4	Sugar, gm.	Plasma, carbon dioxid, per cent	Acetone, mg. for each 100 c.c.	Fat, per cent
I	4	0	48.3	38	155	36	1739	0.76	1119	-24	2844	4.82	+0.7	3.02	1.11	0	0.29			
II	4	0	48.8	40	146	60	1758	0.78	1183	-20	2034	3.61	+2.1	15.29	1.04	0	0.25	47.6		1.66
III	5	0	50.4	45	137	111	1914	0.77	1187	-21	1693	4.41	+2.1	57.78	1.08	0	0.30			
IV	4	15	53.5	45	142	112	1956	0.76	1208	-21	1649	3.58	+2.9	9.46	1.18	0	0.22	58.2	0	1.25
V	6	0	52.7	46	147	112	2004	0.77	1236	-19	1904	5.11	+1.5	76.05	1.12	0	0.29	57.7	0	1.12
VI	4	0	49.3	159	119	41	1919	0.75	1327	-10	2346	19.30	+3.6	76.10	1.40	0		57.8		
VII	2	15	47.3	159	118	41	1907	0.78	1287	-12	1638	19.48	+3.5	47.15	1.29	0	0.28	55.6	0	1.15
VIII	1	0	48.2	159	123	40	1958	0.76	1289	-12	1485	19.43	+3.5	30.30	1.27	0				

Nitrogen balance determined by adding 10 per cent of food nitrogen to urine nitrogen to obtain excreta nitrogen

juice. The plasma carbon dioxid combining power was 17 volumes per cent. Treatment with dietary measures alone accomplished the control of acidosis and glycosuria in fourteen days. The patient was transferred to the metabolism ward for special study September 19.

A man (Case 12, A402817) aged thirty years, had had an acute onset of diabetic symptoms March, 1921. Dietary control was inadequate. There was no history of infections. Weight previous to onset was 160 pounds. The patient was admitted to the hospital August 25. He then weighed 135 pounds. A maximum of 81 gm. of glucose was recovered in the daily urine on an observation diet of carbohydrate 50 gm., protein 60 gm., and fat 60 gm. The urine gave a strong Gerhardt test. The carbon dioxid combining power of the plasma was 26 volumes per cent. The blood sugar was 266 mg. for each 100 c.c. Glycosuria was not controlled after seven weeks of careful dietary manipulation. The patient was transferred to the metabolism ward for special study October 14.

The data recorded in the tables are of special interest in the following particulars: The patient in Case 11 (Table 3) received some of the earlier lots of iletin which was of uncertain strength, some of which were apparently without effect; yet the glycosuria was markedly reduced in Period X. This patient, being the first, in our institution to receive insulin, has been discussed partly for sentimental reasons. The effects of the preparation are less clearly evident than in the other two cases.

The data obtained from Case 2 (Table 4) reveal strikingly the effect of insulin on glycosuria and show also that this is in part dependent on the character of the food. During Period IV there is a very low sugar output, although the diet during the four days of this period was identical to that of the preceding period when, without insulin, the daily urinary glucose averaged 58 gm. The sugar returned to 76 gm. each day in Period V when no insulin was given. In Period VI the diet was readjusted so that it would contain 3 gm. of protein for each kilogram of the patient's body weight and yet remain isocaloric and isosaccharin with the previous diet. It is significant that the effect of the same number of units of the same lot of insulin (Iletin 4660) was appreciably less with this high protein diet than it had been on the low protein, and comparatively higher fat, but isocaloric and isosaccharin diet, also there was a definite increase in the basal metabolic rate. This experiment reinforces certain conclusions drawn from the study of protein feeding in Case A336236 (reported elsewhere).[15] The results emphasize that adjustment of the diabetic diet must be qualitative as well as quantitative. There is accumulating experimental evidence to support the clinical observations of the earlier students of diabetic metabol-

TABLE 5

Summary of Metabolism Experiment 3

Case 12, A402817, A.M., a man aged thirty years, height 170 cm.

Period	Days in period	Iletin dose, units	Weight, kg.	Food				Basal metabolism			Urine						Blood				
				Protein, gm.	Fat, gm.	Carbohydrate, gm.	Calories	Respiratory quotient	Calories, twenty-four hours	Rate, per cent	Volume output, c.c.	Nitrogen in urine, gm.	Nitrogen balance*, gm.	Sugar, gm.	Creatinin, gm.	Diacetic acid, scale 1 to 4	Sugar, gm.	Plasma, carbon dioxid, per cent	Acetone, mg. for each 100 c.c.	Fat, per cent	Amino acid
I	6	0	58.2	36	148	23	1613	0.71	1457	-8	2070	6.58	-1.5	27.4	1.45	0					
II	1	10	57.0	35	146	22	1586	0.72	1437	-8	1920	6.19	-1.2	17.2	1.40	0	0.28	60.1	29.8	1.11	
III	1	15		35	146	22	1586				2135	5.34	-0.3	15.1	1.33						
IV	1	20	56.5	35	173	22	1841	0.72	1525	-3	1780	4.54	+0.5	3.9	1.31		0.20				
V	4	20	57.3	39	203	33	2186	0.74	1487	-5	2018	4.39	+1.1	3.57	1.36	+1 day	0.21	58.0	14.3	0.90	5.5
VI	2	0	56.7	39	200	37	2167	0.73	1491	-4	1895	5.14	+0.5	26.7	1.43	tr. 1 day					
VII	4	30	57.2	50	184	47	2101	0.72	1519	-3	2760	4.89	+2.3	3.47	1.36		0.22	60.4	80.1	0.97	
VIII	1	0		49	161	45	1873				2833	6.54	+0.5	38.3	1.46						

* Nitrogen balance determined by adding 10 per cent of food nitrogen to urine nitrogen to obtain excreta nitrogen

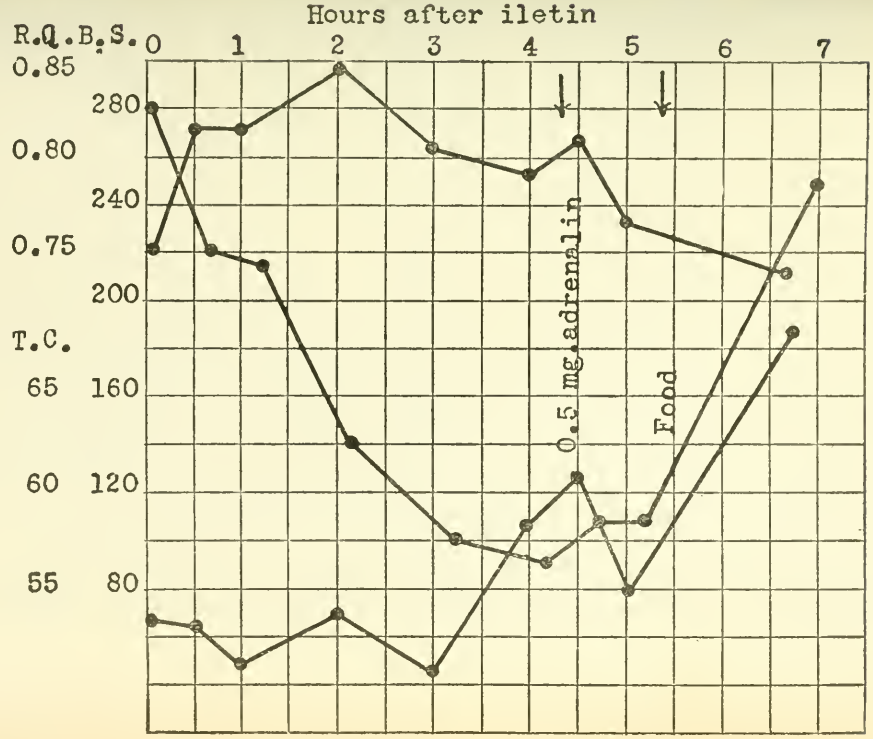
ism in regard to the specifically injurious effect of heavy protein dietaries at least in certain types of cases.

The data from Case 12 (Table 5) confirm a common clinical observation that insulin promptly controls azoturia. In this case the nitrogen balance was negative during the six days of Period I, without iletin, whereas, within two days after the administration of iletin in Period II, the balance was restored. During these two days the diet remained the same as before. Thereafter, and accompanying the increased food allowance, a positive balance persisted although diminishing in Periods VI and VIII, when iletin was discontinued. The high acetone figures obtained in the blood on one occasion during Period VII cannot be accounted for. An error is suggested by the negative acetoacetic acid of the urine of that day.

The basal respiratory quotients and the basal metabolic rates were but little affected by insulin. The same is true of the level of the blood sugar in the blood drawn in the morning. The very high basal respiratory quotients observed in Case 11, both in periods with and without insulin, are curiously anomalous. They recall certain unusual respiratory quotients in diabetes reported by Joslin and by Allen and Dubois.

In Chart 2 are given the results of a study of the effect of insulin on the basal metabolic rate, respiratory quotient, and blood sugar in a diabetic patient who, during the previous seven days in the metabolism ward, had been on a diet of 42 gm. protein, 180 gm. fat and 82 gm. carbohydrate, totaling 2179 calories, together with 10 units of Iletin 725707. The average daily amount of dextrose in the urine was 10 gm. The experiment was carried out with the patient in bed, without food, since the previous evening. After the basal values for the morning were obtained, 20 units of Iletin 725707 was administrered without food. In four hours the blood sugar fell from 282 mg. for each 100 c. c. to 82 mg. for each 100 c. c. There was an immediate rise in the respiratory quotient from 0.75 to 0.82 and after two hours, to 0.85, followed by a gradual fall to 0.79 after four hours. The metabolic rate showed no change until after four hours, at which time the blood sugar was lowest. At the beginning of this fifteen-minute respiration period, the patient said that he felt "fine"; during the period, however, he began to feel uncomfortable, did not look well, and became nervous and agitated. The symptoms were attributable to the falling blood sugar concentration. The agitation was, we believed, the cause of the elevation noted in the metabolic rate. At this time the previous blood sugar determinations were available and plotted. A continuation of the falling blood sugar curve, if maintained, indicated a rapidly approaching dangerous blood sugar level. Therefore, 0.5 mg. of epinephrin was injected subcutaneously. A marked subjective improve-

Case A412868, J.L.C., a man, aged forty years, weight 55.6 kg., height 136 cm., normal basal metabolic rate—18 per cent



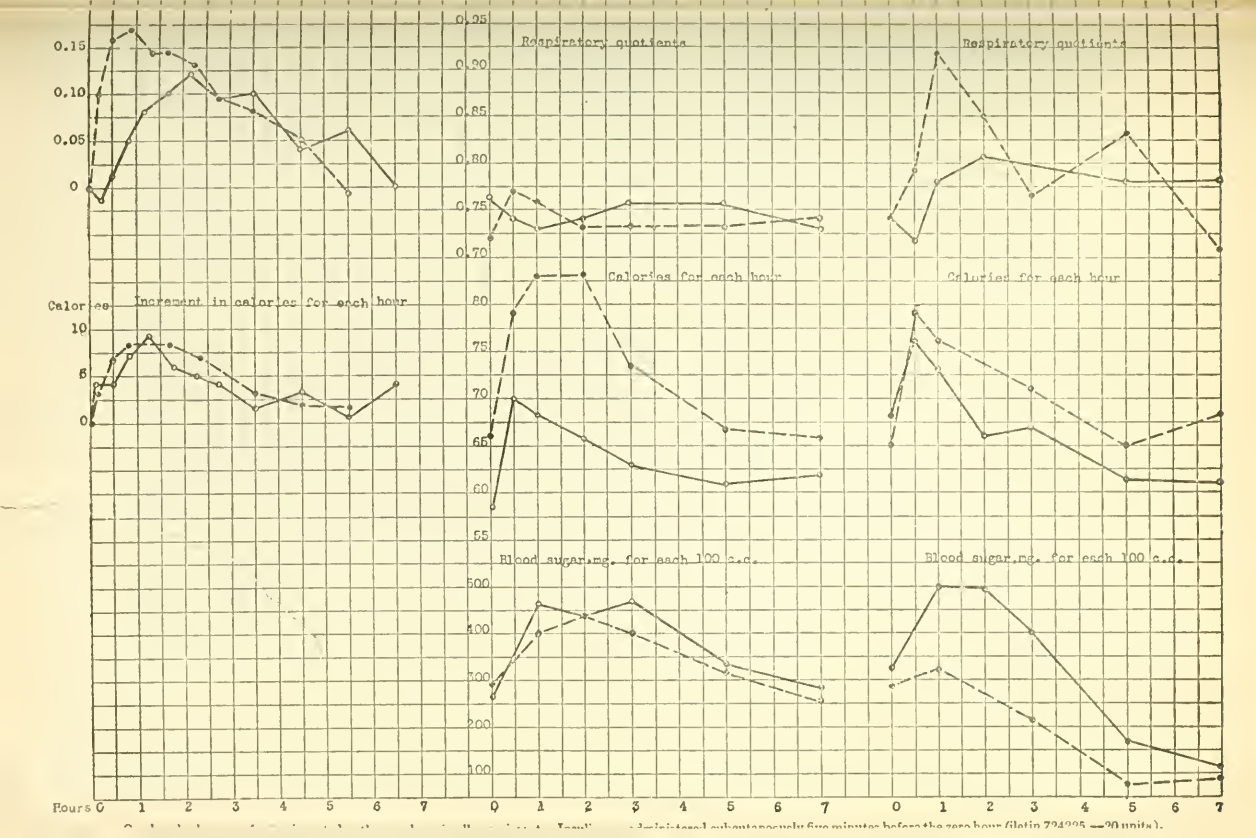
ment immediately followed this injection, being accompanied by a definite increase in the metabolic rate, respiratory quotient, and blood sugar, according to the well-known calorigenic action of epinephrin. In the next period, about forty minutes later, there was a fall in the respiratory quotient and metabolic rate, although the blood sugar was still further increased. The patient was then given one-half of his daily allotment of food. The final determinations, obtained two hours after eating, indicated a definite specific dynamic action of the food and marked rise in the blood sugar but a decrease to practically the original level of the respiratory quotient.

The rapid fall of the blood sugar in the first three hours, with increasing respiratory quotient, indicates the combustion of the excess sugar in the blood; the sharp alteration in the direction of the curve between the third and fourth hours probably indicates a beginning mobilization of sugar, spontaneously occurring at the time of the first subjective symptoms of hypoglycemia. It has occurred to us that this may have been caused by a spontaneous discharge of the patient's own epinephrin and that herein we may be dealing with an automatic protective mechanism against hypoglycemia. The mobilization of sugar was later aided by the administration of epinephrin.

The experiment confirms the value of epinephrin as an emergency measure, as recommended by the investigators at the University of Toronto. It must be immediately followed, however, by the administration of orange juice or some preparation containing a moderate quantity of dextrose, since the calorigenic effect of epinephrin will hasten the combustion of the remaining reserve of glycogen in response to the increased metabolism, so characteristic of this drug.

The evidence from this experiment, as well as from the fact that the daily morning basal level of the metabolism was unaltered by the repeated daily administration of insulin (Tables 3, 4 and 5), indicates that insulin does not have a calorigenic action in the sense either of epinephrin or of thyroxin.

The data of experiments designed to show whether the action of insulin is the same on both dextrose and levulose are presented in Charts 3 and 4. The respiratory quotients, the metabolic rate and the blood sugar level were studied after the administration to diabetic patients of glucose or fructose, both with and without insulin in each case. The patients were young men with reasonably severe, but not complete diabetes. One of them (Case 10, Chart 3) had a tolerance of 48 gm.; the other (Case 13, A363756, Chart 4), a tolerance of 54 gm. glucose as calculated by the method described. Both patients had been receiving reasonably constant diets, about 30 per cent., in caloric value


Increment in calories for each hour
Calories
0.15
0.10
0.05
0
10
5
0
Respiratory quotients
0.95
0.90
0.85
0.80
0.75
0.70
Calories for each hour
80
75
70
65
60
55
Blood sugar, mg. for each 100 c.c.
500
400
300
200
100
Hours 0 1 2 3 4 5 6 7

above their basal maintenance requirements. Both had been receiving iletin for a considerable period.

The procedure with the first subject was as follows: The diet was reduced to the basal maintenance allowance of 1770 calories for a day and iletin was omitted. On the following morning basal determinations of blood sugar, heat production each hour, and the respiratory quotient were obtained. One hundred grams of glucose, dissolved in 500 c.c. of water, was then given by mouth and during the following seven hours a series of data on respiration and blood sugar was obtained. The patient remained in bed during this time, but received one-third of his daily basal food allowance at the conclusion of the experiment. On the next day iletin was again omitted. The third morning the same series of observations was conducted, but iletin was injected immediately before the ingestion of the glucose. The patient then returned for three days to his higher diet and former dosage of iletin and at the end of this interval, the entire procedure was repeated with 100 gm. of fructose in place of the glucose. The procedure with the second patient was the same, except that the fructose tests with and without iletin were made first, and that less powerful iletin was used. The patient in Case 10 (Chart 3) received Iletin 724225 which assayed twice as strong as the preparation 725708 employed in Case 2 (Chart 4). This explains the lower insulin curves in the second series of experiments.

In the charts, the fructose curves have been superimposed on those obtained with glucose. Included in Chart 3, furthermore, are curves drawn from the similar data obtained with normal subjects by Benedict and Carpenter. The essential differences between the behavior of the two sugars which we wish to point out at this time, are the following:

1. In the normal subjects of Benedict and Carpenter (Chart 3), the respiratory quotient was elevated by the ingestion of fructose much more rapidly than by glucose; also considerably higher quotients were obtained with fructose. During the first half hour, there was evidence of depression of the glucose quotient. The specific dynamic action of both sugars was approximately equal in intensity and in time relationship.

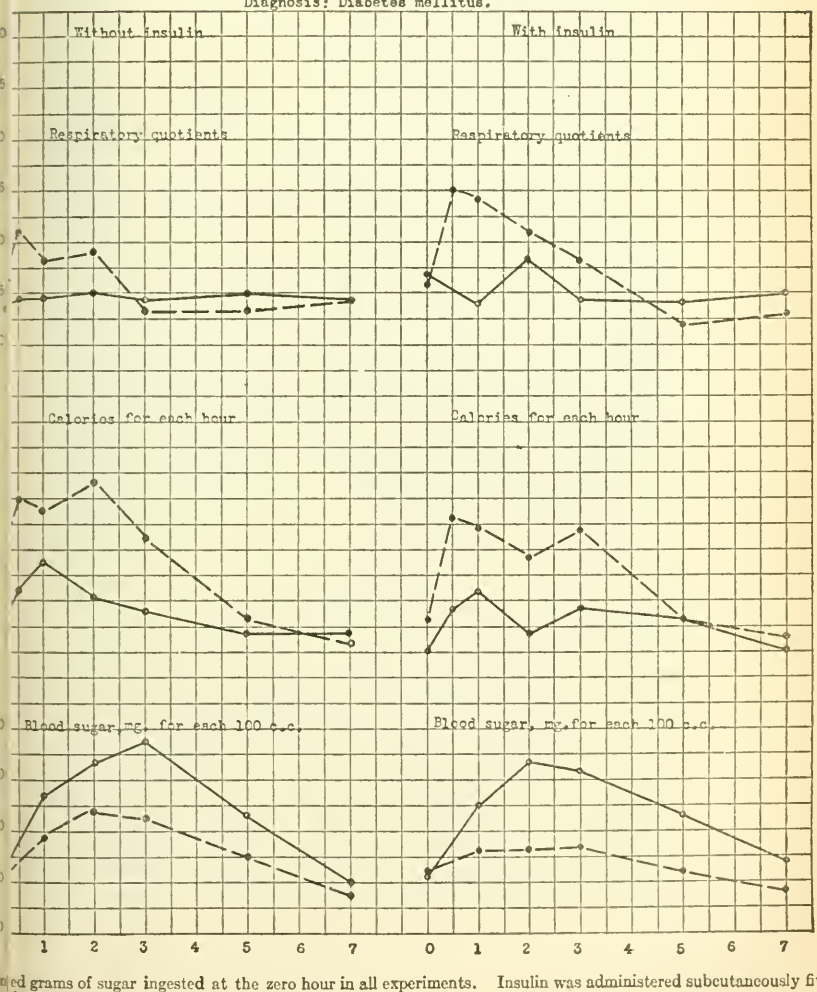
2. In the experiments without insulin on the two diabetic patients here reported, the respiratory quotients show no evidence of elevation after glucose. Instead, in Case 10 (Chart 3) a depression was observed during the first half hour, as was noted in Benedict's and Carpenter's normal subjects. A similar depression in the respiratory quotient, following ingestion of food, was observed and commented on in our previous study.[15] With fructose, no depression occurs and a very slight elevation is noticeable. There is little difference in the specific dynamic

CHART 4

Metabolism of Glucose and Fructose

Case 13, A363756, J.F.R., a man, aged thirty-four years, weight 59.4 kg., height 183 cm.

Diagnosis: Diabetes mellitus.



ed grams of sugar ingested at the zero hour in all experiments. Insulin was administered subcutaneously five fore the zero hour (iletin 725708,—20 units).

Glucose———— Levulose— — —

action of the two sugars, although the fructose curve is the higher. The blood sugar level is elevated about equally by both sugars.

3. In the insulin experiments, the respiratory quotient, after administration of glucose, again showed an initial depression. This was followed, however, by definite but moderate elevation in one case (Chart 3) which began before the end of the first hour. In the second case (Chart 4) the elevation was insignificant. Fructose, however, when accompanied by insulin, caused in both experiments an immediate and very marked rise in the quotient. The specific dynamic action of the two sugars was approximately equal in intensity and in time relationship although, as before, the fructose curve was the higher. The blood sugar was less elevated by fructose than after glucose, and subsequently fell to a lower level.

These results which point to the greater availability of fructose to the organism partially deprived of pancreatic hormone are consistent with the views of Minkowski, and with the work of Newburgh and Embden referred to by him. Recent studies from Embden's laboratory, for instance, have shown that fructose is used more readily than glucose by the excised muscle. In this connection, Isaac has suggested that both glucose and fructose must be converted into their common 1-2 enol before becoming available for metabolism. Fructose is readily converted into this enol, glucose less readily, and Minkowski maintains that the conversion of glucose to this enol is the work of the pancreas. The experiments of Clark, of Hewitt and Pryde, and particularly, the very recent work of Winter and Smith, show that the sugar in normal blood, that is, blood supplied with adequate pancreatic hormone, is not ordinary glucose, but some form of sugar, presumably more sensitive than glucose. Winter and Smith, Hewitt and Pryde suggest that the sensitive substance is gamma glucose and that the action of insulin is to convert glucose into this sensitive gamma form. It occurs to us that still another possibility should be considered. It is well known that dilute alkali will throw glucose into the 1-2 enol. It is also well known that the action of alkali in Fehling's solution is exerted on the sugar to sensitize it for oxidation, this being easily demonstrated by potentiometer experiments with oxidation-reduction cells. Is it not probable that insulin goes beyond the action of alkali and brings the sugar into a new reactive form more available for oxidation and polymerization than the 1-2 enol? According to

one of the views expressed by Nef, the formation of lactic acid, which the work of the Embden and Hopkins schools has shown so definitely to be at least one of the routes over which sugar is catabolized, probably depends on the production of the 3-4 enol. This substance splitting at the double bond would yield two 3 carbon atom chains and thus two molecules, one or both of which might be glyceric aldehyde from which lactic acid could be easily formed. The fact that neither fructose nor glucose will burn in the completely diabetic organism, while with small concentrations of insulin, fructose burns and glucose still fails to burn, seems to support this view. It is evident that the CO group in fructose is one step nearer the 3-keto hexose which would give the 3-4 enol, than is the CO group in glucose and it will be interesting to see whether further evidence will support this view. In any case, it seems fairly clear that the action of insulin is to convert the stabile sugars into some highly sensitive material and that its effect is like that of a carburetor interposed in the gas line of an internal combustion engine, preparing the explosive material, but not, like a detonator, actually exploding the charge.

The studies reported are so diverse that it is difficult to draw a brief summary, or to record the conclusions in detail. There seems to be no question regarding the very definite effect of insulin on sugar metabolism and we are convinced of its great value in the treatment of the more severe forms of diabetes and in the emergencies of this condition (acidosis, infection, and so forth).

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A CLINICAL STUDY OF THE EFFECTS OF INSULIN IN SEVERE DIABETES

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The published studies of Banting, Best and Macleod have shown conclusively that the extract of the pancreas as prepared by this group of investigators affords relief not only to experimental diabetic animals, but also to humans afflicted with the disease. In its general application to the problem of human diaebetes there are many questions to be solved: indeed, the limitations and possibilities of the extract can only be determined by an extended accurately controlled clinical study. Through the courtesy of Professor Macleod and his associates and the Eli Lilly Company the writer has been privileged to carry on such an investigation for several months in the clinic at the Highland Hospital.

Before one can measure the value of a remedy in the treatment of diabetes mellitus, there must first be learned what can be gained by the proper application of diet, rest and regulation of personal hygiene. The remarkable results attained by dietary control are well known, accordingly in an evaluation of the effects of pancreatic extract upon a given case or series of cases the immediate and ultimate significance of dietary regulation as a factor must be kept clearly in mind. To the clinical investigator various methods are available for measuring the efficacy of a remedy in diabetes; namely by means of the respiratory quotient, the use of the blood sugar level and the estimation of glucose utilization by contrasting the glucose content of the diet with that of the urine. Each of these methods is of value and in a critical research all should be employed. In this investigation chief reliance is placed upon the glucose utilization method because over long periods of time it is the most trustworthy.

To bring out more clearly the value and possibilities of dietary regulation the writer has tabulated 100 moderately severe and severe cases studied in the clinic during a period of three years from January, 1919, through December, 1921. The

cases were of the type of those to whom insulin has been given. In the following tables are summarized the data which are of interest. As a measure of the severity of these cases it may be said that thirty-three cases are dead, six cannot be accounted for and are probably dead, sixty-one are living and their condition known.

TABLE 1. *Time necessary to acquire a maximum food tolerance and maintain a normal blood sugar level.*

41	cases	2 weeks
32	"	3 "
18	"	4 "
4	"	5 "
5	"	6 to 8 "

Thus it will be seen that 41 cases under careful dietary control required a period of two weeks before they gained the maximum food tolerance and the remaining cases in the series an even longer stay.

TABLE 2. *Glucose utilization gained by 100 cases diabetes by dietary regulation alone in a hospital stay of from 2 to 8 weeks.*

5	cases	25 to 50 grams
19	"	51 " 75 "
38	"	76 " 100 "
27	"	101 " 125 "
11	"	126 plus

From the foregoing it will be seen that even severe cases may acquire a fair ability to metabolize glucose and still maintain a normal blood sugar level. The glucose content of these diets is calculated by the method proposed by Woodyatt and includes not only the carbohydrates but the fraction yielded by protein and that assumed to be available from fat.

TABLE 3. *Showing gain or loss of glucose utilization at end of 6 months and 1 year, data on 48 cases.*

	After 6 Months	After 1 Year
Utilization unchanged	15 cases	6 cases
Gain 25 per cent.	13 "	2 "
" 26-50 per cent.	2 "	2 "
Loss 25 per cent.	5 "	16 "
" 26-50 per cent.	4 "	6 "
" 51-75 " "	1 "	
" 76 plus per cent.	1 "	

An examination of this table shows the ability to utilize glucose in 15 cases 6 months after leaving the hospital had not changed; in 6 cases it remained unchanged at the end of 1 year. In 13 cases there was a gain of approximately 25 per cent. at the end of 6 months, but the gain persisted in only 2 cases for 1 year. Two cases showed a gain of more than 25 per cent. In all, 15 cases showed a gain in food tolerance at the end of six months and at the end of one year the number had decreased to 4 cases. After 6 months 11 cases showed a loss of tolerance, the number increasing to 22 cases at the end of 1 year. It is obvious that in diabetes one is dealing with a progressively declining function in the great majority of cases and in spite of all dietary regulation. This becomes the more evident if one examines the thirty-three dead cases in this series. Of these, thirty-one died from diabetic exhaustion and two from complications.

TABLE 4. *Ages of 31 cases dying from diabetic exhaustion.*

2 cases	Up to 6 years
1 case	6 " 10 "
3 cases	11 " 15 "
2 "	16 " 20 "
2 "	21 " 30 "
8 "	31 " 40 "
9 "	41 " 50 "
5 "	51 plus "

TABLE 5. *Duration of diabetes of 28 cases dying from diabetic exhaution.*

3 cases	Less than 1 year
10 "	Between 1 and 2 years
7 "	" 2 " 3 "
6 "	" 3 " 4 "
1 case	" 4 " 5 "
1 "	7 years
2 cases	10 "
1 case	20 "

The majority of the above cases lived on diets designed to keep the blood sugar within normal limits and to keep the urine sugar free. In many cases this was impossible, the pancreatic function apparently becoming completely exhausted with death closing the scene. Some of the cases had struggled

for years with the disease, others were of a more acute or malignant type and succumbed rapidly. An understanding of these important features of diabetes is basic in any attempt to interpret the influence of insulin on the course of the disease. Moreover, these factors must be reckoned with in the administration of the pancreatic extract.

To restate briefly the thoughts brought out in the foregoing tables: it requires from 2 to 4 weeks to determine the food tolerance of the average unregulated diabetic. Under proper conditions such a patient may acquire the ability to utilize a very considerable amount of glucose. If the patient adheres rigidly to a suitable program, his tolerance may increase over a period of a year or more and he may retain the tolerance for many years. With many diabetics the function declines rapidly in spite of all dietary regulation in which case the tenure of life is brief.

It was from a group of failing diabetics that the cases for this study of the effect of insulin were recruited. In all 41 cases have been treated with extract. Of these 9 cases were definitely in coma when the administration of the extract was begun. A second group of 12 cases were practically exhausted and were in a perfectly hopeless stage so far as help from any dietary procedure was concerned. A third group of 15 cases, while very severe, were living on very low diets and might have survived for a few months under suitable conditions. A fourth group of 8 cases were much less severe in character, nevertheless they had definite limitations which made life irksome.

Case histories with all laboratory data gathered on these cases would make this report far too voluminous for publication. Typical examples from each group have been selected and will be presented in brief form as evidence of the general characted of the cases studied and treated.

Coma Cases. Nine were treated; six survived and three died. The first two deaths can be directly attributed to insufficient insulin. So long as it was available the patients improved, but relapsed into coma when no more insulin was to be had. The third case died from an associated septicemia and sapremia due to a progressive moist gangrene on the stump of an amputated limb. Of the six surviving cases, the following are illustrations.

Case 4513. Female, 43 years. Diabetes of 11 years standing. Onset of coma with severe vomiting which lasted for 48 hours. Had been having large doses glucose by mouth, rectum and intravenously. Patient in profound coma for 12 hours when first seen. Blood sugar 454 mg. Plasma bicarbonate 19.5 volumes per cent. In the first fifteen hours patient was given 128 units of potent extract, but still remained profoundly comatose. During the next day 96 units of potent extract were administered. During the latter part of this day the patient became somewhat brighter but not enough to recognize her family. On the following morning 24 units were given and this served to correct the acidosis and relieve the coma. This patient was completely comatose for 48 hours, and drowsy for approximately 24 hours additional. The patient is now getting a diet of about 1800 calories, receives 20 units of extract daily and has remained well for eight weeks. In each case the insulin treatment was supplemented by the injection of salt solution per rectum, intravenously and by mouth when possible.

Case 3489. Female, 34 years. Duration of diabetes 2 years. Admitted to hospital in profound coma. Had been comatose for several hours prior to admission, attributed to a hypnotic. Blood sugar 280 mg. Plasma bicarbonate 24 volumes per cent. During first 9 hours 132 units of potent extract given intramuscularly. In the following 24 hours 60 units given, which not only served to bring the patient out of coma, but also to lower the blood sugar to 49 mg., producing a slight reaction which made the intravenous injection of 20 grams glucose necessary. Patient made a good recovery. Diet was adjusted to 2000 calories, later reduced to 1800 calories, which she is able to utilize when given 25 units of insulin daily. This patient has remained well for eight weeks. The remaining 4 cases in this series are doing well.

The second group might well be called the precoma type. All of the twelve cases in this group presented some of the early signs of coma as air hunger, postration, vomiting and epigastric pain. They did not become unconscious, however, before treatment was begun. They represent diabetics who have been treated for long periods of time and must be regarded as being almost entirely without pancreatic function so far as sugar metabolism is concerned. The following cases are cited as illustrative.

Case 1524. Male, 22 years. Duration of diabetes 7 years. As indicative of the prolonged severity, on January 28, 1918, patient had a blood sugar of 280 mg. Since that time the blood sugar has been uniformly high in spite of low diets. During the year 1918 and until recently his diet has only rarely exceeded 1000 calories. For months at a time it has not been more than 800 calories. For more than 3 years he has not had a blood sugar lower than 200 mg., nor has his 24-hour urinary ammonia been less than 2 grams, averaging more than 3 grams. Frequently during this time it has exceeded 5 grams.

At the age of 15 years he weighed 97 pounds net; at 22 years his weight had dropped to 74 pounds, part of which was due to edema. On May 17, 1922, when insulin treatment was begun, he was a most pitiable spectacle. Blood sugar 450 gm. Plasma bicarbonate 24.9 volumes per cent. For weeks the patient had suffered severely from pains in his legs, which made the constant use of codeine necessary The edema and profound weakness confined him to bed and he was rapidly approaching death, when through the great kindness of Doctors Banting and Macleod, extract was supplied for his treatment. The restoration of this patient to his present state of health is as achievement difficult to record in temperate language. Certainly few recoveries from impending death more dramatic than this have ever been witnessed by a physician. This patient has now been having extract for 300 days. During the months of December, 1922, and January, 1923, he has been on a daily diet of 1360 calories containing 97 grams glucose. On this his utilization has varied from a negative balance to positive balance of 95 grams. His carbohydrate utilization has depended upon several factors, variation in the potency of the extract, time and number of injections daily and gain in body weight. It is probable also that his pancreas has become more exhausted for if extract be omitted for a single day there is complete failure to metabolize carbohydrates so far as can be told from clinical tests. His daily blood sugar after breakfast and before extract is given ranges from 300 mg. to 380 mg. After injections it frequently drops to 90 mg., then rapidly mounts to the higher figures. The greatest improvement in the case is in his appearance and general well being. This cannot be measured in figures or well stated in words. To keep this patient alive is a critical challenge to the efficacy of insulin.

A second example of unusual severity is worth recording.

Case 4341. Male, 34 years. Duration of diabetes 4 years. Admitted to clinic February 1, 1922, with a blood sugar of 330 mg. Alveolar air 24.8 mm., total urinary ammonia 6.2 grams. For two months patient was kept on diets averaging less than 800 calories. During this time his blood sugar had a range of from 200 mg. to 310 mg. averaging 250 mg. daily. The 24-hour urinary ammonia ranged from 2 grams to 8 grams daily, averaging more than 3 grams daily. Sugar was constantly present in the urine. From April to September his diet was slightly increased and the evidences of metabolic failure became correspondingly greater, the blood sugar being constantly above 300 mg. and the urinary ammonia ranging above 4 grams daily. The patient suffered greatly from general body pain and from edema. His condition when the use of insulin was begun on September 7 was hopeless. Body weight had declined from 95 pounds on admission to 91 pounds, part of which was edema. He has now been under treatment 145 days. When the patient was recently discharged from the hospital he had been for 10 days on a diet of 1765 calories containing 112 grams glucose. His daily utilization was approximately 100 grams. His weight had increased to 114 pounds and he feels strong and well. He is now receiving 25 units of extract daily in two doses. Practically

the same story could be written about all of the cases in this group. They represent the type which has been juggled by dietary procedure to the extreme limit of their pancreatic capacity. Any measure which adds to the comfort of this class of cases, even though it be temporary, must be regarded as an advance in treatment.

The third group of 16 cases were of unusual severity. They were all physically incapacitated for work and were permanent invalids. An illustrative case is as follows:

Case 4367. Male, 36 years. Duration of diabetes 4 years. Strict diet for two and one half years; last year diet abandoned. Bedridden for one year. Physical examination negative except for profound emaciation, as shown by body height of six feet and net weight 87 pounds. On admission blood sugar was 500 gm. Plasma biscarbonate 26.3 volumes per cent. After cautious dieting for 6 weeks, patient was able to take 1660 calories containing 90 grams glucose daily and was free from glycosuria. The diet was then increased until it contained 106 grams glucose and the patient was given daily, with an occasional miss, 10 units of insulin for 34 days. The average daily glucose utilization increased from 90 to 100 grams, a rather severe edema which characterized his condition from the beginning practically disappeared and there was a noteworthy gain in strength. For the next 5 days insulin was discontinued, during which time the glucose utilization dropped to 67 grams. For the next 30 days with a daily dose of 10 units of insulin the glucose utilization averaged 100 grams. The patient then became mentally depressed and refused further treatment. In the succeeding days there was a progressive fall in glucose utilization from 97 to 29 grams. His weight had increased during the treatment from 97 to 29 grams. His weight had increased during the treatment from 87 to 97 pounds. The patient exhibited a degree of cachexia, languor and loss of appetite which suggested some other complicating disease, as malignancy. It could not be demonstrated however. This case was the most unsatisfactory one of the series. Attention is called to the fall in glucose utilization when insulin is discontinued and discussed elsewhere in this study.

Of the cases of diabetes of moderate severity eight were studied. These were patients who were obliged to live on from 1200 to 1600 calories of food daily to keep the blood sugar normal and the urine sugar free. They did not have the marked physical weakness which charaterized the other groups. The following is a good example.

Case 1577. Female, 59 years. Duration of diabetes 14 years. For past 7 years has lived on regulated diet with very gradual decline in tolerance. On admission to clinic patient had a blood sugar of 230 mg. and a glucose utilization of approximately 75 grams, which was not improved by 8 days of diet regulation. Insulin treatment was then instituted, 10 units daily for one week, then 20 units daily for eight days. The diet was increased from 1420 calories to 1830 calories and the glucose utilization increased from 75 to 125 grams with a

corresponding improvement in well-being and strength. The vision of this patient was quite impaired by the so-called diabetic retinitis, so that only large objects could be seen. After the improvement in the nutrition following the use of insulin therapy the vision improved demonstrably.

Of the 44 cases reported in this series, sixteen since their discharge from the hospital have been carrying on the treatment in the home for a period of several weeks or sufficiently long to give some notion of the practicability of home treatment. Of the sixteen cases, five have not done well, it being necessary in each instance both to lower the diet and increase the quantity of extract. Eleven cases have maintained the gain in diet due to the insulin and seem to be improving in strength and well-being. Practically all of them have gained slightly in weight. Four deaths have occurred, three of them being coma cases already referred to. The fourth death was due to acute dilatation of the heart from overexertion and in no way related to the diabetes or insulin administration.

Some of the most difficult questions relating to insulin therapy have to do with the size of the dose, time and frequency of administration. Macleod and his associates have shown that the reaction occasioned by the extract is very precipitous, lasting not more than three to four hours. In clinical diabetes it is desirable to have it extend over as much of the day as possible. The relation of the dose to the ingestion of food is important. It has been urged that the best time to give the extract is that which will bring about the greatest activity of the extract at the height of the period of digestion when the absorption of the greatest amount of carbohydrates is taking place. As a rule, this means that the extract should be given either before or immediately after a meal. Whether the daily amount thought necessary should be given in one or more doses is a difficult question to answer. The usual objections to hypodermatic medication obtain with insulin and make it desirable to have the administration no more frequent than is absolutely necessary. With very severe cases one dose does not appear to be sufficient. If a sufficiently large dose to keep the patient urine sugar free be given, reactions are likely to occur. The patient may remain urine sugar free in the day time, but during the night will excrete very considerable amounts of sugar. When the two doses are given daily, reactions are less likely to occur and the night urine sugar

output is less. There will be found periods in the day with both the single and the double dose method when the blood sugar level is high. In order to determine the value of doses of varying frequency, the following tests were made.

Two cases of severe diabetes were selected who had been on a constant diet for several days with a definite amount of insulin and whose glucose utilization was also constant. The tests lasted over a period of four days. On each day the urine was carefully saved and accurately measured every 2 hours from 7 o'clock in the morning until 9 o'clock at night and until 7 o'clock the following morning. Sugar determinations were made daily on bloods removed at 7:30 and 11 A. M. and 4 and 9 P. M. The meals were served at 8 A. M., 12 M., and 5 P. M. On the first two days three doses of extract were given immediately after the serving of each meal. With one case, of the total quantity of extract, one-half was given after breakfast and one-fourth after each of the other meals. In the second case, three-fifths of the dose was given after breakfast and one-fifth at each of the other meals. On the third day of the test, in one case one-half of the quota was given at breakfast and the remainder at supper. In the other case, two-thirds was given in the morning and one-third at the evening meal. On the fourth day, one large dose was given in each case at the morning meal. In one case the daily quantity was reduced from 40 to 30 units because of the fear of reaction. In the other case the dose was unchanged. A study of the curves of this investigation show clearly that when the daily quota is given in three divided doses and at the meals a fairly uniformly low blood sugar curve is maintained and the urine sugar outgo is negligible. In one patient the advantage of three over two daily doses is more striking than in the other case. The advantage of either three or two doses over a single large dose is apparent in either case. It would be even more striking if the single dose test were to be continued into the second day, for then the effects of the insulin given at night on the previous test days would not obtain and the night urine sugar outgo and the morning blood sugar would be much higher.

Similar tests have been made on three other cases and confirm the belief that in severe cases a greater degree of glucose utilization is obtained, reactions occur less frequently and probably less insulin is needed if the extract be given in three properly spaced doses instead of either one or two administrations. Furthermore, it is probable that both the pancreas and tissues are protected against the deleterious effects of sustained high blood sugar levels.

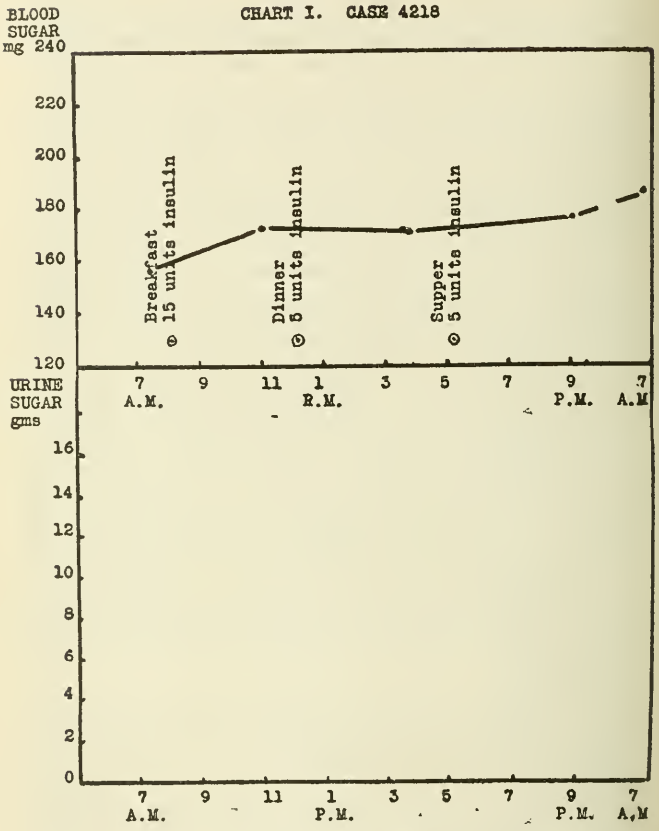


Chart I, Case 4218. First test. Showing effects of insulin administration, THREE DOSES during day, on blood sugar curve and urine sugar outgo. The fairly uniform slightly elevated blood sugar curve and absence of urine sugar should be noted.

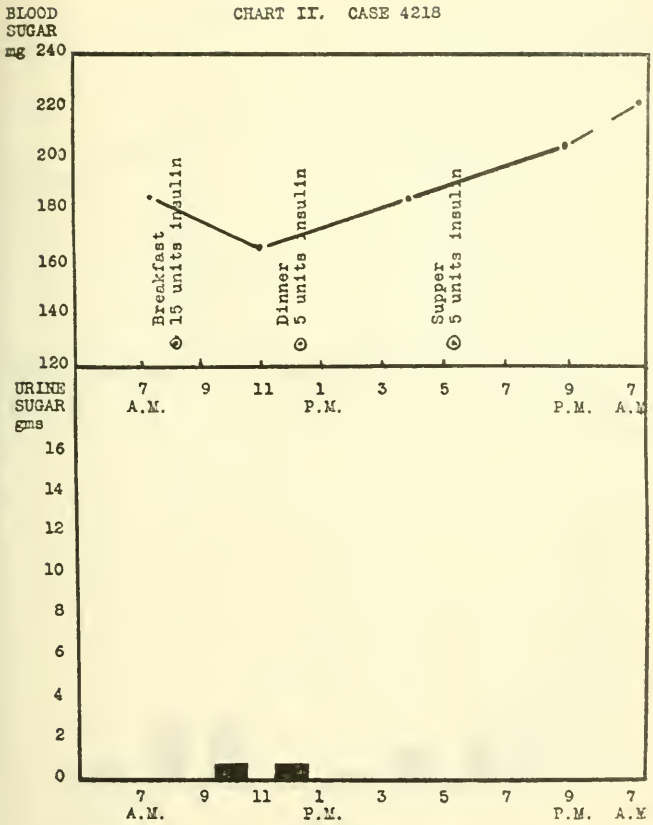


Chart II, Case 4218. Second test. Showing effects of insulin administration, THREE DOSES during day, on blood sugar level and urine sugar outgo. The fairly uniform blood sugar curve at a moderately high level, also a change in the renal sugar threshold is noted. The total urine sugar output in this 24 hours was 2.8 grams.

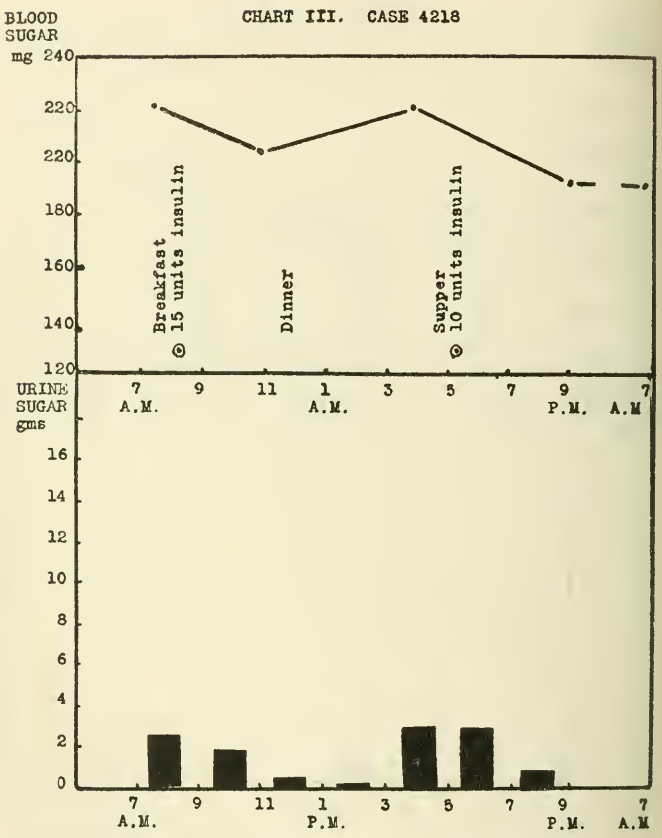


Chart III, Case 4218. Third test. Showing effects of insulin administration, TWO DOSES during day, on blood sugar curve and urine sugar outgo. Note the higher blood sugar level maintained and the constancy of urine sugar during the 2 hour periods. Total urine output 14 grams.

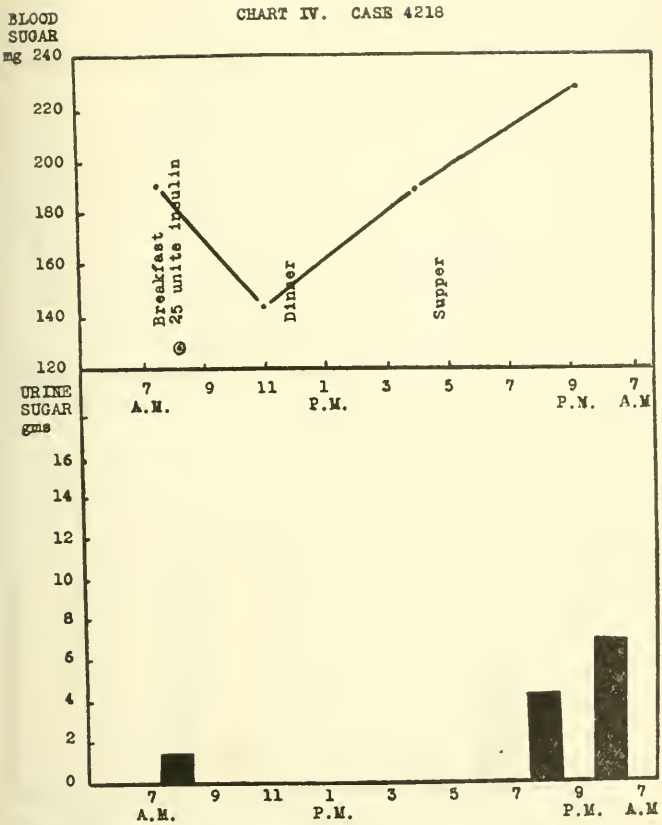


Chart IV, Case 4218. Fourth test. Showing effects of insulin administration, ONE DOSE during day, on blood sugar curve and urine sugar outgo. Note the prompt drop in the blood sugar curve 3 hours after administration and the sharp rise during the rest of the day. Urine sugar output 14 grams.

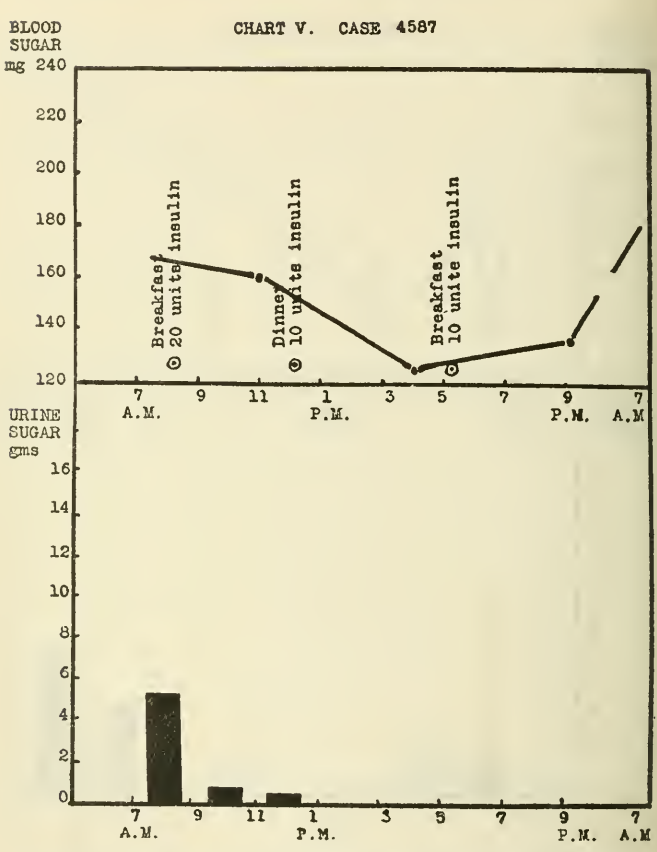


Chart V, Case 4587. First test. Showing the effects of insulin administration, THREE DOSES during day, on blood sugar curve and urine sugar outgo. Note the low blood sugar curve and the low renal sugar threshold during the earlier hours of the day. Total urine sugar output 5 grams.

CHART VI. CASE 4587

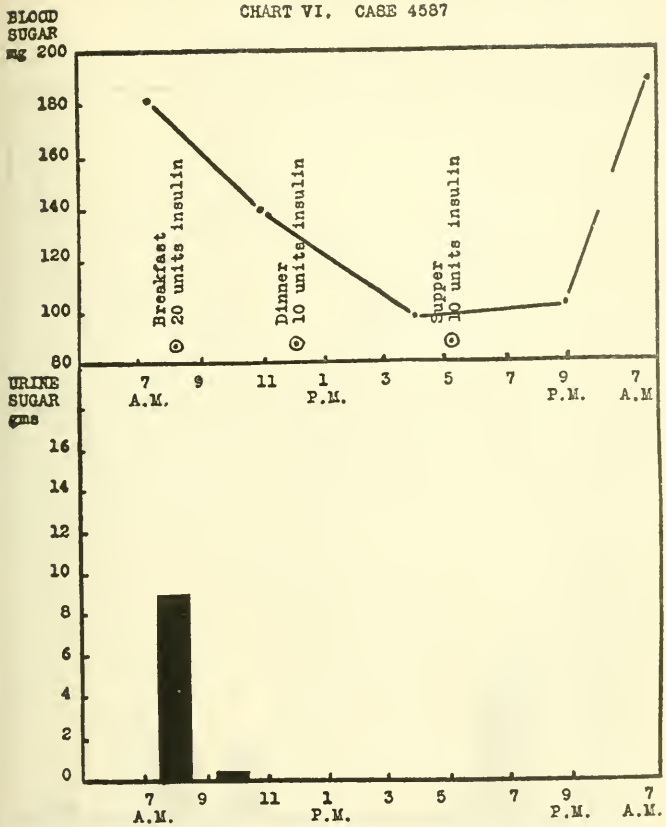


Chart VI, Case 4587. Second test. Showing effects of insulin administration, THREE DOSES during day, on blood sugar curve and urine sugar outgo. Note the high morning blood sugar level suggesting that part of the glucose from the previous day was held in storage by the presence of the Insulin and was released during the night. Urine sugar output 9 grams. It is a common experience to have patients on insulin treament go through the day with an approximately normal blood sugar level and to be urine sugar free indicating that glucose is either stored or burned or both during the day period. During the night hours the blood sugar level rises often beyond the renal sugar threshold so that variable amounts of sugar will be found in the early morning sample and the blood sugar will be found high. This suggests that some of the glucose stored during the day is released at night when no insulin is present, either to prevent its liberation or promote its combustion.

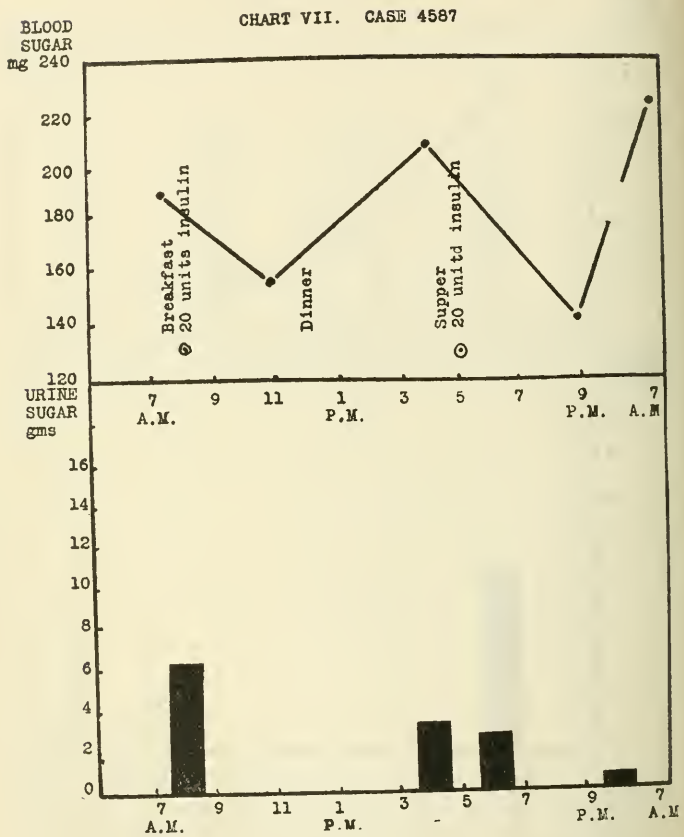
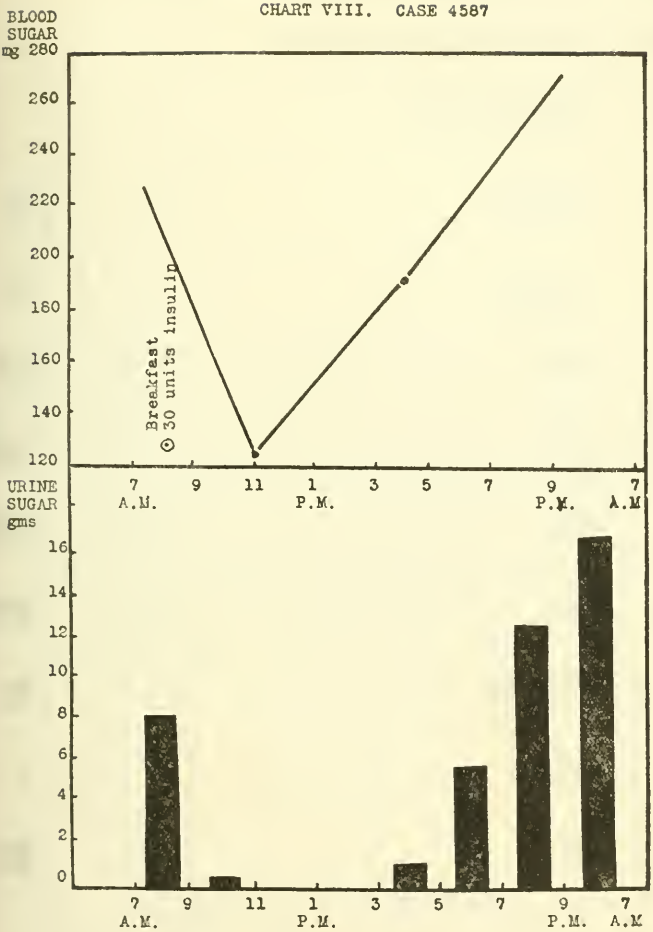


Chart VII, Case 4587. Third test. Showing the effect of insulin administration, TWO DOSES during day, on blood sugar surve and urine sugar outgo. Note the marked variations in the blood sugar curve and its higher level, also the presence of considerable amounts of urine sugar during the day. Total urine output 15 grams.

CHART VIII. CASE 4587



Case VIII, Case 4587. Fourth test. Showing effects of insulin administration, ONE DOSE during day, on blood sugar curve and urine sugar outgo. Note the sharp drop in three hours in blood sugar from the one large dose and the equally sharp rise following, with large amount of sugar in the urine. The total urine sugar output 44 grams.

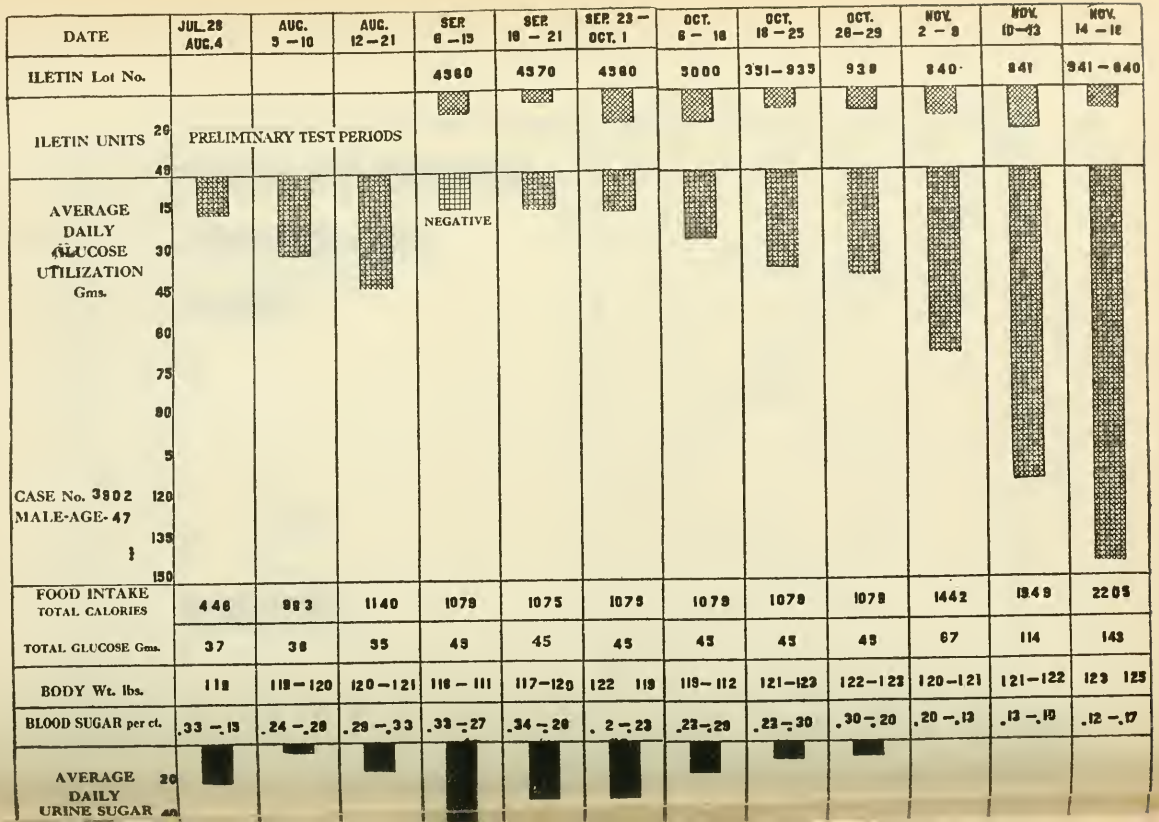

DATE
JUL. 28 AUG. 4
AUG. 5 — 10
AUG. 12 — 21
SEP. 8 — 15
SEP. 16 — 21
SEP. 23 — OCT. 1
OCT. 6 — 16
OCT. 18 — 25
OCT. 26 — 29
NOV. 2 — 8
NOV. 10 — 13
NOV. 14 — 18
ILETIN Lot No.
4360
4370
4380
5000
351 — 935
938
940
941
941 — 840
ILETIN UNITS
20
40
PRELIMINARY TEST PERIODS
AVERAGE DAILY GLUCOSE UTILIZATION Gms.
15
30
45
60
75
90
NEGATIVE
CASE No. 3802
MALE-AGE- 47
5
120
135
150
FOOD INTAKE TOTAL CALORIES
446
983
1140
1079
1075
1079
1079
1079
1078
1442
1949
2205
TOTAL GLUCOSE Gms.
37
38
55
45
45
45
45
45
45
67
114
143
BODY Wt. lbs.
118
118 — 120
120 — 121
116 — 111
117 — 120
122 119
119 — 112
121 — 123
122 — 123
120 — 121
121 — 122
123 125
BLOOD SUGAR per ct.
.33 — .15
.24 — .28
.28 — .33
.33 — .27
.34 — .28
. 2 — .23
.23 — .28
.23 — .30
.30 — .20
.20 — .13
.13 — .10
.12 — .17
AVERAGE DAILY URINE SUGAR
20

Chart IX, Case 3902. A severe case of diabetes, showing gain in glucose utilization due to insulin administration. During the preliminary periods patient was tested on low diets at different levels to determine the maximum glucose utilization without insulin. The food level was then raised and insulin treatment begun. Various batches of extract were tested, each for a period of several days. The average daily glucose intake and urine sugar outgo for each period was then determined and plotted. The blood sugar range and other data during each period is also shown. It will be noted that the patient underwent constant and quite marked improvement indicated by the fact that the best glucose utilization without insulin was from August 12 to August 21, a daily average of 44 grams, with a blood sugar range of 0.29 to 0.33 per cent. on a diet of 1140 calories, while at the end of the insulin test period on a diet of 2200 calories there was an average daily utilization of 143 grams with practically a normal blood sugar curve and no urine sugar, with a gain in weight of 4 pounds and a very great gain in strength and well-being.

Reactions. In only one case did a serious local reaction result. This occurred in case 1524 with extract procured from the University of Toronto in the early stages of their work and before the technic of purification had been perfected. The extract at this time was quite irritating and frequently caused areas of induration about the site of injection. In two instances in the above case these indurated areas developed into sterile abscesses which had to be opened and which slowly healed. Since then several thousand doses of the extract have been given without local reactions and but one accident, a mother breaking off a needle in the skin of her son, which was not recovered, but which has caused no ill effects. In two cases anaphylactic reactions have been experienced which are worth noting.

Case 1524 for several months was given the extract prepared by the University of Toronto from the pancreas of beef animals. Later, when the preparation of the Lilly Company was substituted, which is made from pancreas of the pig, the patient experienced promptly most severe anaphylactic reactions which apparently cannot be overcome. All attempts to use highly purified and practically protein-free extract have proved futile and have had to be abandoned. The following is a description of the phenomenon observed after an injection of the pork material September 23, 1922. Patient apparently normal, no pruritus, urticaria or edema evident. Five cubic centimeters insulin injected intramuscularly. Three minutes later patient stated that upper lip felt stiff and swollen, followed rapidly by dry mouth. In ten minutes lips became greatly swollen. Small wheals then appeared on all parts of the body. The reaction increased in violence for two hours, during which time the wheals became larger and coalesced No nausea or vomiting occurred. Patient very weak and prostrated. Heart sounds rapid, regular, clear. Lungs normal. Adrenalin, 15 minims subcutaneously and atropine sulphate one-one hundreth grain by mouth were given, affording slight relief. Twenty-four hours later patient had recovered from the reaction, but was very weak. The weakness and prostration persisted for four days. During this time much skin exfoliated from various parts of the body. It is interesting to note that this patient has been having beef extract since May 17, 1922, to February 1, 1923. It has been administered daily except for a period from July 7 to 20, when it was discontinued because of local abscesses. Since then there have been occasional days when it has not been given. The patient has exhibited no evidence of sensitivity against beef material, which dispels the fear one time entertained that he might become sensitive to this and other proteins and make the administration of the extract a difficult problem.

One other case, a child seven years of age who had a complicating inactive hilum pulmonary tuberculosis, exhibited a slight sensitivity

to pork extract. An attempt was made to overcome it by continuing the administration of the extract twice daily for several days. The reaction, however, became more severe, and the pork extract was abandoned for extract made from the beef, with a complete disappearance of the symptoms and a gain in the patient's general condition.

After patients have been treated with insulin for a period of time, will increasingly large doses be necessary to maintain the carbohydrate metbolism? This question is intimately bound up with the question whether or not the function of the pancreas may improve or retrogress during treatment. These and other questions relating to the permanent value of insulin treatment cannot be answered without giving due regard to the facts pointed out in the opening chapters of this study, namely: the ability of the unaided diabetic pancreas to recover when proper dietary adjustments are made. And since some diabetics make quite marked recoveries and maintain their improvement for long periods of time, while others either gradually or rapidly decline, conclusions as to the efficacy of insulin may be quite in error unless cases be selected whose food tolerance is more or less stationary or fixed. Even this fixed type is not free from difficulties in such a study because when cases which formerly were required to live on low diets are now fed higher diets by reason of insulin administration, a very considerable gain in body weight occurs, increasing the food requirements of the individual and thus altering one of the basic factors or premises of the problem. Thus far, from this clinic 12 cases have been treated from 60 to 2500 days. Of these, five cases have been under treatment for five months or more. All were very severe cases at the onset. It is extremely improbable that any of them would have survived if the extract had not been administered. In the case of each individual in this group, it has been necessary to practically double the amount of extract required when the treatment was first instituted. In each case, however, there has been a gain in weight of from 15 to 25 pounds and an even greater gain in strength. In three of the cases there has been a gain of several fold in the ability to utilize glucose, while in the other two the gain has been variable and prac-

*Since the writing of this article, two months previously, it has been necessary to either lessen the dose of extract or increase the diet in several cases, indicating permanent improvement in pancreatic function or more potent extract, probably the former.

tically negligible. In several other cases treated for shorter periods of time and notably children, it has been found necessary gradually to increase the dose from twenty to fifty per cent. This would indicate a gradual failure in pancreatic function. In none of the 43 cases studied in this clinic has evidence been observed to support the belief that the natural function of the pancreas has been increased by the use of insulin. The decline in function noticed in the majority of the cases suggested by the necessity for gradually increasing the dosage indicates the necessity for the continuance of the careful dieting and along the lines of careful regulation suggested by Allen, Joslin, Woodyatt and others. No constancy has been found between the number of units of insulin administered and the amount of glucose which may be utilized.

Conclusions: 1. In the study of any remedy for the treatment of diabetes, the significance of dietary control must be thoroughly evaluated, because with proper regulation diabetics may gain and maintain to a very considerable degree the ability to utilize glucose.

2. It requires from 2 to 4 weeks of careful observation and dieting to determine approximately the maximum diet which will enable a diabetic to maintain a normal blood sugar level and urine free from glucose.

3. If proper dietary control be continued, the diabetic may gain slightly in food tolerance over a period of a year or more or he may decline with more or less rapidity in that time.

4. Because of the foregoing facts, it is difficult to measure with precision the value of insulin in diabetes.

5. A series of 44 cases were studied over periods of time varying from 20 to 250 days. Of these 37 were unusually severe, nine cases being in coma when treatment was begun. The food tolerance of 34 cases had been carefully determined by previous study.

6. Four deaths have occurred. Two of these can be directly attributed to insufficient insulin, and two were from causes unrelated to the diabetes.

7. The 40 living cases have gotten along with far greater comfort and strength than was experienced before the institution of the insulin treatment.

8. The feeding of high diets and attempting to make their utilization possible by large doses of insulin has not been satisfactory.

9. The best treatment, apparently, is a diet which will enable the patient to meet the energy requirements of light work with sufficient insulin to insure the metabolism of the food.

10. Time and frequency of dosage are important. Apparently the action of extract lasts only for a few hours. In severe cases it should be administered at least twice and better three times a day in properly spaced doses.

11. To prevent reactions a higher blood sugar level should be permitted than is customary when extract treatment is not employed.

12. The first effect of insulin apparently is to cause the storage of glucose. Later it may in part be burned. During the night glucose appears to be released from the tissues, leading to a high morning blood sugar and often urinary sugar.

13. Diabetic patients receiving insulin treatment experience a noteworthy gain in strength and well-being which suggests that the body is served in other ways than in the improvement in carbohydrate metabolism.

14. Experience to date does not warrant the conclusion that the natural function of the pancreas in cases of severe diabetes is either increased, regenerated or diminished because of the use of the extract.

FOOTNOTE: The extract used in this study was furnished through the courtesy of the Eli Lilly Corporation of Indianapolis and bears the trade name Iletin.

THE EFFECT OF INSULIN ON THE METABOLISM OF DIABETES.

REGINALD FITZ, M.D., WILLIAM P. MURPHY, M.D., AND SAMUEL B. GRANT, M.D.
FROM THE MEDICAL CLINIC OF THE PETER BENT BRIGHAM HOSPITAL, BOSTON.

INTRODUCTION.

Since October 1st, 1922, the Peter Bent Brigham Hospital has, upon the recommendation of the University of Toronto, received a weekly supply of insulin from the Eli Lilly Company of Indianapolis made by them under the trade name of Iletin. The insulin was given this hospital by that concern for purposes of investigation through the kindness of Dr. G. H. A. Clowes and Dr. A. L. Walters of the Eli Lilly research department. This paper records certain clinical studies which have been so far completed here to add to the data already reported concerning the immediate effect of the new drug upon the metabolism of diabetes mellitus. The results confirm those already reported by Banting and associates.

The cases with which this paper deals were selected from all the diabetics entering the hospital after October first either because they appeared to be particularly severe or because they seemed suitable for some special observation which we wished to make. They remained in open wards during their period of study and were fed from the general diet kitchen by prescription diets filled from standard food tables and prepared according to customary dietetic measures. The insulin was injected subcutaneously in each instance under our personal supervision so that no mistakes in dosage or method of administration were made. We injected the patients receiving insulin two or three times each day between one hour or one and one-half hours before meals except the coma cases in which we made use of more frequent injections. The dose administered varied according to the needs of each case. No general reactions were encountered even after large doses and no infections developed. A few patients complained of transitory soreness at the site of injection which lasted

for a few hours. One patient who was given one of the earlier lots of insulin seemed sensitive to it and developed a raised erythematous patch at the point of each injection, which later became a tender wheal finally fading away and disappearing about forty-eight hours after its beginning. Cutaneous skin tests using the protein of pork, beef and horse serum as well as insulin failed to show that the patient was sensitive to these proteins.

The urine and blood analyses were made by the following methods: twenty-four hour urine specimens, or single specimens in a few cases, were collected and analyzed each day for sugar by Benedict's qualitative and quantitative methods and for diacetic acid by the ferric chloride test. The total nitrogen excretion was determined by Kjeldahl's method and the total acetone body excretion by Van Slyke's method. The blood analyses were made on oxalated blood samples drawn, except in specified cases, in the morning before breakfast and within a few minutes of the first insulin injection. They were analyzed for sugar by Folin's method, for total acetone by Van Slyke and Fitz' method, and for the plasma CO_2 combining power by Van Slyke's method. The respiratory quotient and basal metabolism determinations were made on patients in the post absorbtive state with a Tissot spirometer and Haldane gas analyses according to the technique outlined by Boothby and Sandiford. Two nine-minute periods were used for each experiment and the average respiratory quotient and heat production so obtained was considered the true one. No attempt was made to calculate the non-protein respiratory quotients on account of the objections raised to such calculations in experiments of this type by Wilder, Boothby and Beeler.

We controlled our results as well as possible by following the effect of the withdrawal of insulin upon the blood, urine and respiratory metabolism of individual cases and by contrasting the clinical course in hospital of comparable cases of diabetes treated with and without the new drug. The results of this study are tabulated.

The Effect of Insulin on the Respiratory Quotient and Basal Metabolism.

Respiratory quotient and metabolism experiments were performed on four cases according to the following plan: A single determination was made shortly after the patients entered the

TABLE 1

The Effect of Insulin on the Respiratory Quotient and Basal Metabolism.

P. B. B. H. Medical No. 19482. A man 38 years old with diabetes of one year's duration.

Date	Food Intake				24 Hour Specimen of Urine	Blood	Respiratory Metabolism				Remarks
	Carbohydrates	Protein	Fat	Total Calories	Glucose	Sugar per 100 c.c.	Total Calories for Each Hour	Basal Metabolism (Du Bois Standard)	Respiratory Quotient	Weight	
1922	gm.	gm.	gm.		gm.	gm.		%		kg.	
Sept. 23.	Unmeasured. 100 gm.	Contained at least Carbohydrates			Single Specimen 2.2%	.33	57.9	− 1	.69	44.0	
Nov. 8.	45	75	135	1695	0	.24	53.7	−12	.78	48.1	8 Units of insulin on previous day.
Nov. 23.	76	76	210	2498	0	.24	57.7	− 6	.75	49.0	12 Units of insulin on previous day.
Dec. 5.	76	76	210	2498	30.0	.27	59.5	− 3	.72	49.0	No insulin for previous three days.

hospital. At this time the urine was not sugar free and there was always a marked hyperglycemia. We felt that these facts made no difference in the interpretation of results because we were concerned solely with the food materials being oxidized in the body at the time the tests were made. After the necessary data were obtained the patients were given insulin for a considerable period of time until each was ingesting a reasonably large caloric diet and was excreting no sugar in the urine. One or two metabolism determinations were now made. In two cases the tests were made in the morning before insulin was injected, and in two cases about an hour after the morning injection but before any food was eaten. Finally, in three cases the insulin was withdrawn for at least three days to allow the effect of the drug to pass off and another metabolism determination was made. The results of these studies are found in Tables I, II, III and IV.

TABLE I.

In this case the chief interest centres upon the effect of insulin on the respiratory quotient. This rose from .69 at entry to .78 and .75 while the patient was under the influence of insulin, but later fell to .72 after the drug was omitted for three days. If the average of the quotients obtained without insulin is compared with that found when insulin was being administered, one notices an average rise from .705 to .765 and can assume from these figures that while nearly all of the calories oxidized to meet the basal caloric requirements of the individual were derived from protein and fat without insulin, approximately twenty per cent. were derived from carbohydrate combustion when the drug was being injected.

The second case studied confirms this finding. The data are recorded in Table II.

TABLE II.

As can be seen the respiratory quotients increased during the insulin period. The quotients obtained, however, were considerably higher than in the first case. We believe this is due to the fact that they were determined shortly after the morning injection of insulin. The third quotient estimated three days after insulin was omitted was still well above the base line. This suggests that insulin, besides acting immediately after its introduction into the body may continue to be active for some time after

TABLE II

The Effect of Insulin on the Respiratory Quotient and Basal Metabolism.

P. B. B. H. Medical No. 19661. A woman 33 years old with diabetes of 20 months' duration.

Date	Food Intake				24 Hour Specimen of Urine	Blood	Respiratory Metabolism				Remarks
	Carbohydrates	Protein	Fat	Total Calories	Glucose	Sugar per 100 c.c.	Total Calories for Each Hour	Basal Metabolism (Du Bois Standard)	Respiratory Quotient	Weight	
1922	gm.	gm.	gm.		gm.	gm.		%		kg.	
Oct. 26. .	22	13	18	302	0	. . .	31.4	−38	67	49 0	30 Units of insulin on previous day.
Nov. 26. .	104	63	150	2018	0	.20	44.5	−20	83	49 0	10 units on morning of test.
Dec. 6. .	105	81	180	2364	0	13	45 8	−15	.86	46 7	18 Units of insulin on previous day. 6 units on morning of test.
Dec. 13. .	106	82	200	2552	65.0	.23	47.5	−11	77	44 4	No insulin for previous three days.
1923											
Jan. 2. . . .	35	60	200	2180	10.5	.27	48.5	−7	.73	42.6	No insulin for previous fourteen days.

TABLE III

The Effect of Insulin on the Respiratory Quotient and Basal Metabolism.

P. B. B. H. Medical No. 19940. A woman 18 years old with diabetes of 4 months' duration.

Date	Food Intake				24 Hour Specimen of Urine				Blood		Respiratory Metabolism				Remarks
	Carbohydrate	Protein	Fat	Total Calories	Nitrogen	Glucose	Acetone Bodies as Acetone	Nitrogen Balance	Sugar per 100 c. c.	Acetone Bodies as Acetone per 100 c. c.	Total Calories for Each Hour	Basal Metabolism (Du Bois Standard)	Respiratory Quotient	Weight	
1922	gm.	gm.	gm.		gm.	gm.	gm.	gm.	gm.	gm.		%		kg.	
Nov. 29. .	80	57	42	926	9.30	81.70	4.10	− .20	.23	.025	54.4	+ 3	.68	40.8	10 Units insulin on day previous.
1923															
Jan. 11. .	80	70	210	2490	7.35	0	0	+3.85	.20	0	47.2	−11	.75	41.3	45 Units insulin on day previous.
Jan. 16. .	80	70	150	1959	8.60	42.30	0	+2.60	.26	0	50.0	− 5	.77	39.9	No insulin for three days.

it is no longer given. The fourth determination made after the patient had been fourteen days without insulin was much lower. The progressive rise in basal metabolism observed in this case is somewhat misleading as the patient was edematous when the studies were begun so that the body weight figures are inaccurate. Moreover the patient received small amounts of thyroid extract each day after November thirtieth. The total metabolism was definitely increased by this treatment, as shown by the increasing number of calories oxidized per hour, although there is no reason to doubt that the high respiratory quotient figures obtained were due to insulin.

TABLE III.

Striking effects were again obtained on the respiratory quotient by insulin in the case reported in Table III where again the quotient remained elevated for at least three days after the drug was omitted although the blood sugar concentration increased and glycosuria returned. At the first examination the patient was losing nitrogen as judged by the nitrogen balance but began to store nitrogen while under the influence of the drug. Apparently the withdrawal of insulin affected protein metabolism as well as carbohydrate storage and oxidation because the patient excreted an increased amount of nitrogen in the urine as soon as the injections were stopped. We did not complete the experiment as the patient had pulmonary tuberculosis and we felt that it was unjustifiable to allow the diabetes to continue untreated for too long a period.

TABLE IV.

The case reported in Table IV was the most severe of the group studied in this fashion. At the time of the first observation the D to N ratio was approximately 3.06 = 1, the patient was losing 3.81 gm. of nitrogen a day in the urine, and there was a mild acidosis. Furthermore the patient had been undernourished for several months so that the basal metabolism was very low. Insulin caused a rise in the respiratory quotient, the nitrogen balance became positive, the acidosis and glycosuria disppeared, and the fasting blood sugar concentration diminished. The rise in respiratory quotient was most marked in the last experiment which followed the injection of insulin. As the diet was increased the total calories oxidized each hour to meet the basal metabolic needs were increased and coincidentally the basal metabolic rate rose slightly.

TABLE IV

The Effect of Insulin on the Respiratory Quotient and Basal Metabolism.

P. B. B. H. Medical No. 20040. A boy 14 years old with diabetes of 15 months' duration.

Date	Food Intake				24 Hour Specimen of Urine					Blood		Respiratory Metabolism				Remarks
	Carbohydrate	Protein	Fat	Total Calories	Nitrogen	Glucose	Acetone Bodies as Acetone	D.:N. Ratio	Nitrogen Balance	Sugar per 100 c. c.	Acetone Bodies as Acetone per 100 c. c.	Total Calories for Each Hour	Basal Metabolism Rate (Du Bois Standard)	Respiratory Quotient	Weight	
1922	gm.	gm.	gm.		gm.	gm.	gm.		gm.	gm.	gm.		P.Ct.		kg.	
Dec. 13	22	31	41	581	8.76	48.8	5.50	3.06	−3.81	.25	.037	31.9	−40	.72	25.4	No insulin.
Dec. 20	30	50	40	680	9.15	41.6	.93	1.27	−1.15	.27	.024	33.2	−40	74	27.7	20 Units insulin on day previous.
1923																
Jan. 9	42	50	135	1583	5.74	5.0	Trace		+2.26	.20	Trace	35.5	−35	78	27.2	34 Units insulin on day previous.
Jan. 26	30	50	110	1310	4.02	8.5	Trace		+3.98	.17	Trace	41.0	−27	.87	28.6	30 Units insulin on day previous. 10 units before metabolism test.

On the whole the effect of insulin on the respiratory quotient and basal metabolism of the four cases was uniform and striking. In each case the quotient rose several points after insulin had been injected showing that more carbohydrate was being oxidized when the drug was being used than when it was not. This observation was controlled in two cases by the withdrawal of insulin and coincidental fall in the quotient. The highest quotients obtained were in the two cases in which the determinations were made shortly after insulin was injected, pointing to an almost immediate action of the drug. On the other hand, in two cases the quotient remained elevated for at least three days after insulin was no longer introduced into the body, suggesting either carbohydrate storage through insulin previously given or a prolonged effect of insulin on carbohydrate oxidation. Two cases with a negative nitrogen balance came promptly into nitrogen equilibrium and then began to store nitrogen in the body during the time that insulin was given. Two cases with a lowered basal metabolic rate showed an increasing metabolism during the period of observation. This may have been due in one case to thyroid extract but was probably due in the other to the increased food ingested. There was no reason for believing that insulin had any effect upon the basal metabolism except indirectly.

The Effect of Insulin on the Blood Chemistry of Cases with Severe Acidosis.

It is a well known fact that cases on the verge of coma have a high concentration of sugar and of acetone bodies in the blood, a low alkali reserve as judged by the plasma bicarbonate and usually a large excretion of sugar, nitrogen and acetone bodies in the urine. The cause of these findings is generally conceived to depend upon inability of the organism to oxidize glucose. As a result, such sugar as is present in the body or is formed from protein katabolism is excreted, and fat, being imperfectly burned in the absence of glucose, is converted into acetone, diacetic acid or betahydroxybutyric acid with resultant acidosis. Since insulin appears to make possible the immediate oxidation of glucose in an organism otherwise incapable of utilizing it, the administration of the drug should check the formation of acetone bodies in severe diabetes and therefore should be of great value in the treatment of acidosis and coma. We have had opportunity to study its effect in four cases.

TABLE V.

This case illustrates the effect of insulin on the blood chemistry in very severe acidosis as the patient appeared moribund when first seen and was given no dietetic treatment except forced fluids. The blood sugar and acetone body concentration fell in a

TABLE V

The Effect of Insulin on the Blood Chemistry of a Case of Diabetic Coma.

P. B. B. H. Medical No. 20064. A woman 64 years old with diabetes of six years' duration entered the hospital December 14, in coma. Given forced fluids. Broncho-pneumonia at necropsy.

Hours After Admission	Blood			Insulin
	Sugar per 100 c.c.	Acetone Bodies as Acetone per 100 c.c.	Plasma Carbon Dioxide	Units Subcutaneously
	Gm.	Gm.	Vol. per Cent	
0	.84	.139	11.9	5
1½	.84	.120	....	10
3½	....	....	....	10
5½	.73	.073	13.9	10
7½	.60	.081	17.8	10
11½	.52	.063	18.7	20
16½	.41	.081	21.4	20

striking fashion and the alkali reserve increased after the drug was administered. The patient died in about eighteen hours. At necropsy a bronchopneumonia was found which may have been an important factor in causing death.

TABLE VI.

This case again shows the effect of insulin upon the blood sugar and acetone body concentration in severe acidosis and again demonstrates that the drug is active even in the presence of severe infection. The blood sugar and acetone figures both fell after the treatment was begun, the diminution in the blood acetone being especially remarkable. Coincidentally the concentration of sugar and acetone in the urine diminished although that of nitrogen increased. The increasing nitrogen excretion was probably due to the increased protein destruction of infection as the patient had a high fever during life and the post-mortem blood culture developed a growth of streptococcus hemolyticus.

Similar studies in regard to the effect of insulin upon the

TABLE VI

The Effect of Insulin on the Blood and Urinary Chemistry of a Case of Diabetes Complicated by Acidosis and Gangrene.

P. B. B. H. Medical No. 20128. A man 58 years old with diabetes of three years' duration. Gangrene of both feet of three months' duration with rapid spread of gangrene of five days' duration. Given fluids, orange juice and oatmeal gruel. No operation. Septic spleen at necropsy. Heart's blood grew streptococcus hemolyticus.

Date	Urine			Blood		Insulin
	Nitrogen per Liter	Glucose per Liter	Acetone Bodies as Acetone per Liter	Acetone Bodies as Acetone per 100 c.c.	Sugar per 100 c.c.	Units Subcutaneously
1922	Gm.	Gm.	Gm.	Gm.	Gm.	
Nov. 23....	5.23	41.6	5.26	.138	.40	10
Nov. 24....	8.35	45.5	3.32	.047	.22	30
Nov. 25....	8.80	38.4	1.97	.045	.31	30
Nov. 26....	11.35	21.8	.93	.032	.27	50

concentration of acetone in the blood and its excretion in the urine were obtained in two less severe cases. The data are recorded in Tables VII and VIII.

TABLE VII.

In this case the diet was constant for two days before insulin was injected and for three days after. The patient excreted large amounts of sugar and acetone bodies before insulin was injected, and the blood acetone concentration after an initial slight fall

TABLE VII

The Effect of Insulin on the Blood and Urinary Acetone of a Case of Diabetes with Moderate Acidosis.

P. B. B. H. Medical No. 19940, a woman 18 years old with diabetes of four months' duration.

Date	Food Intake				24-Hour Specimen of Urine		Blood		Remarks
	Carbohydrate	Protein	Fat	Total Calories	Glucose	Acetone Bodies as Acetone	Sugar per 100 c.c.	Acetone Bodies as Acetone per 100 c.c.	
1922	gm.	gm.	gm.		gm.	gm.	gm.	gm.	
Nov. 25.....	102	60	15	783	87.5	19.15	.27	.056	
Nov. 26.....	77	57	42	914	60.0	16.00	...	....	
Nov. 27.....	77	57	42	914	125.0	16.32	.26	.040	
Nov. 28.....	...	..	..	...	.....	.....	.29	.046	Before insulin
Nov. 28.....	77	57	42	914	81.7	4.10	...	....	10 Units insulin
Nov. 29.....	77	57	42	914	20.0	1.40	.23	.025	16 Units insulin
Nov. 30.....	77	60	40	900	17.9	1.36	...	....	16 Units insulin
Dec. 1.....		..	..	...	.....	.....	.24	.017	

was increasing. The immediate effect of insulin upon the sugar and acetone excretion was particularly striking; within twenty-four hours the blood acetone concentration fell from 46 mgm. per 100 c. c. of blood to 25 mgm. The acidosis continued to clear up rapidly under further treatment so that four days after the first injection all danger of acidosis was past and the glucose excretion per twenty-four hours upon a constant diet had fallen from 125 gm. to less than 20 gm.

TABLE VIII.

In this case a slightly different plan of treatment was adopted. We followed Joslin's Diabetic Diet Sheet for seven days and included a two-day fast before using insulin. Under this form of treatment the patient's urine did not become sugar free; the acidosis did not clear up entirely as evidenced by the excretion of acetone bodies in the urine, and there was an actual increase in acetone formation within the body as manifested by an increasing blood acetone concentration. We then began giving the patient increasing amounts of fat on a constant carbohydrate-protein

TABLE VIII

The Effect of Insulin on the Blood and Urinary Acetone of a Case of Diabetes with Moderate Acidosis.

P. B. B. H. Medical No. 20333, a man 36 years old with diabetes of at least two years' duration.

Date	Food Intake				24-Hour Specimen of Urine			Blood		Remarks
	Carbohydrate	Protein	Fat	Total Calories	Glucose	Acetone Bodies as Acetone	Nitrogen	Sugar per 100 c.c.	Acetone Bodies as Acetone per 100 c.c.	
1923	gm.	gm.	gm.		gm.	gm.	gm.	gm.	gm.	
Jan. 21	189	89	15	1247	195.0	10.58	12.20	.23	.035	
Jan. 22	102	58	0	640	133.0	13.90	13.85	...	....	
Jan. 23	64	33	0	388	107.5	10.82	13.85	.23	.053	
Jan. 24	36	27	0	252	50.0	9.61	8.55	...	....	
Jan. 25	15	5	0	80	41.0	7.23	10.00	...	.065	
Jan. 26	Fast	Day	..	....	19.0	4.75	5.25	...	....	
Jan. 27	Fast	Day	..	....	25.0	10.80	7.23	.19	.063	
Jan. 28	22	13	18	302	12.0	5.33	4.15	...	....	5 Units insulin
Jan. 29	30	40	50	730	6.4	2.50	5.55	.17	.063	9 Units insulin
Jan. 30	30	40	60	820	9.1	1.36	4.66	...	...	9 Units insulin
Jan. 31	30	40	80	1000	6.7	1.33	4.17	.17	.033	11 Units insulin
Feb. 1	30	40	90	1080	....	....	....	...	....	12 Units insulin
Feb. 2	30	40	100	1180	8.4	1.80	6.90	.19	.035	12 Units insulin
Feb. 3	30	40	100	1180	5.4	1.22	5.33	...	....	15 Units insulin
Feb. 4	30	40	110	1270	Trace	.56	5.57	...	....	15 Units insulin
Feb. 5	30	40	110	1270	0	Trace	6.32	.17	.022	17 Units insulin

level, and injecting increasing doses of insulin. The glycosuria and acetonuria disappeared and the acetonemia became much lessened.

Although other factors than insulin probably helped to cause the findings obtained in this particular instance, this case also serves to illustrate another effect of the drug which has impressed us in nearly all the cases which we have treated; namely, its sparing effect, when first injected, upon the excretion of nitrogen. During the seven days before this patient received insulin he excreted in the urine 71 gm. of nitrogen on a diet containing 212 gm. of protein or approximately 34 gm. of nitrogen. During the eight days covered by our data following the insulin injections he excreted in the urine 43 gm. of nitrogen on a diet containing 293 gm. of protein or approximately 47.0 gm. of nitrogen.

Summary and Conclusions.

On the whole, therefore, the evidence accumulated from the study of the cases reported here in regard to the effect of insulin on the metabolism of diabetes confirms in every way that already brought forward by Banting, Best and their associates. We found in four cases of diabetes that insulin caused a definite increase in the fasting respiratory quotient. The quotients were highest in the two cases receiving insulin shortly before the tests were made, suggesting that the effect of the drug was almost immediate. On the other hand elevated respiratory quotients were obtained in two cases three days after the drug was no longer being injected, suggesting that the effect of insulin does not immediately wear off. We studied the blood chemistry of two cases of severe diabetic acidosis complicated by infection. In each of these cases, insulin appeared to cause a remarkable fall in the blood sugar and acetone body concentration. We believe that the result obtained depended upon the fact that insulin enabled these patients to oxidize glucose and therefore checked the formation of acetone bodies within the tissues. Two less severe cases of acidosis are reported which were treated with insulin. In each of these glycosuria and acetone body formation and excretion diminished rapidly following the injection of the drug. Finally, we have called attention to the fact that insulin appears to influence protein katabolism in diabetes, enabling the diabetic organism to store nitrogen instead of excreting an amount equal to or greater than that ingested. In brief, since

insulin enables patients with severe diabetes to oxidize glucose, since it checks the formation of acetone bodies, and since it spares protein, it undoubtedly is a drug of the greatest practical value for treatment, especially of those diabetics with low carbohydrate tolerance, severe acidosis and extreme emaciation or weakness.

It gives us the greatest pleasure to thank the Eli Lilly Company, Dr. Clowes and Dr. Walters for their generosity and kindness in supplying us with the insulin used for this work.

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THE USE OF INSULIN IN JUVENILE DIABETES.*

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When in August, 1922, insulin† first became available for clinical use at the Presbyterian Hospital, there was very little information at hand to guide us in employing it in the therapeutic care of human diabetes.

The isolation of insulin from the pancreas of dogs and its effect in reducing the sugar in the urine and blood of diabetic animals had been beautifully demonstrated by Banting and Best. These same observers with their co-workers at Toronto University had also been successful in isolating insulin from the pancreas of other mammals, notably the cow and the hog. They had also achieved convincing therapeutic results in the treatment of some twenty odd cases of human diabetes, over periods ranging from two to six months. The Toronto workers, however, had been handicapped by many factors, chief among them being:

1. Intermittent shortage of insulin supply and the consequent necessity of interrupting treatment.

2. Local abscesses at sites of injection of insulin. (Insulin having to be given hypodermically.)

3. Sensitization phenomena due to the relatively high protein content of the material injected, and,—

4. Inadequate dietary facilities.

It can, therefore, be seen that although much had been accomplished, there still remained several fundamental problems in the clinical application of insulin to human diabetes, which had to be solved before it could be claimed that insulin was a specific method of therapy, effective in all types of the disease.

It seemed to us of crucial importance in this connection to determine whether certain of the maximally severe types of diabetes, as, for instance, the type observed in children, could be successfully treated, with arrest of the downward progress of the disease,

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† The material used was "Iletin" as supplied by the Eli Lilly Co., Indianapolis, Indiana, whose cooperation throughout the work we wish to acknowledge.

and the establishment of a sufficient food intake to bring about growth and gain in weight. It was this problem that we decided to work on.

Fortunately, the clinical material at our disposal has been adequate, and the present report deals with the use of insulin in a group of diabetic children, nine in number, whose ages range from two years to sixteen years. The nature of the diabetes in all of these patients was that extremely severe form of this disease whose inherent downward nature has been so universally recognized:—a form which has hitherto resisted all types of therapy.

It has been our aim to show that: (1) with insulin treatment continuously applied, the carbohydrate and total food tolerance could be definitely increased, with a corresponding decrease of sugar in the urine; (2) continuous gain in body weight could be achieved; (3) insulin could be given continuously over long periods of time, without ill effects and with maintenance of a caloric intake up to or nearly up to the normal level. These conditions, if attained in the severest forms of human diabetes, seem to us convincing proof of the therapeutic specificity of insulin.

Naturally, the program outlined involved the determination of more or less important details of procedure, such as technique of administration of insulin, number of doses given per day, and their time relation to food, the amount of insulin which could be tolerated in a given case an don a given carbohydrate intake, the number of grams of carbohydrate which could be oxidized in the presence of a given number of units of insulin, the duration of insulin effects after given doses had been administered, the effect upon ketosis, and many other details which had as yet received little or no controlled study.

This paper deals, however, only with the major problem as stated above. We purpose to present our data in the form of brief narative case histories descriptive of the course of the diabetes prior to the time that insulin was given, while the course of each case subsequent to the giving of insulin is portrayed in the graphic charts and occasional photographs that follow.

EXPLANATION OF DATA ON CHARTS.

In all cases the laboratory work was done in a uniform manner. Blood sugar was determined by the method of Folin and Wu; urinary sugar by the Benedict quantitative method; urinary nitrogen by the macro-Kjedahl method. The nitrogen intake was considered equivalent to food protein divided by 6.25. Available carbohydrate was calculated differ-



Case III Before Insulin



Case III After Insulin



Case III Before Insulin



Case III 5 Mos. After



Case III Before Insulin



Case III 5 Mos. After



Case VI Before Insulin



Case VI 4 Mos. After



Case VI Before Insulin



Case VI 4 Mos. After



Case VI Before Insulin



Case VI 4 Mos. After



Case VII Before Insulin



Case VII 3 Mos. After



Case VII Before Insulin



Case VII After Insulin



Case VII Before Insulin



Case VII After Insulin

ently according to whether the patient was in positive or negative nitrogen balance:—When the nitrogen balance was positive, or when the urinary nitrogen was not determined, the available carbohydrate was taken as equivalent to the food carbohydrate plus 0.58 times the food protein. When the nitrogen of the urine exceeded that of the food (negative balance), then the available carbohydrate was taken as equivalent to the food carbohydrate plus 3.65 times the urinary nitrogen. "Utilized carbohydrate" (as it appears on the charts) is equal to available carbohydrate minus urinary carbohydrate (glucose). Available carbohydrate does not appear on the charts as a separate entity, but is, of course, the sum of the utilized carbohydrate and urinary carbohydrate. All the recorded weights were taken in the morning after the bladder was emptied and before breakfast. Blood sugars were also taken before breakfast, and before the first dose of insulin. The values entered on the charts are the average daily amounts of each substance calculated by the week. Thus, the value given for utilized carbohydrate in any week is the average of the seven daily amounts for that week. Blood sugar values are an exception to this rule, in that they usually represent single determinations. In the cases where only qualitative glucose determinations were done on the urine, the available (not the utilized) carbohydrate appears on the chart, while urinary sugar is roughly represented by the average daily number of plus signs as determined by qualitative tests.

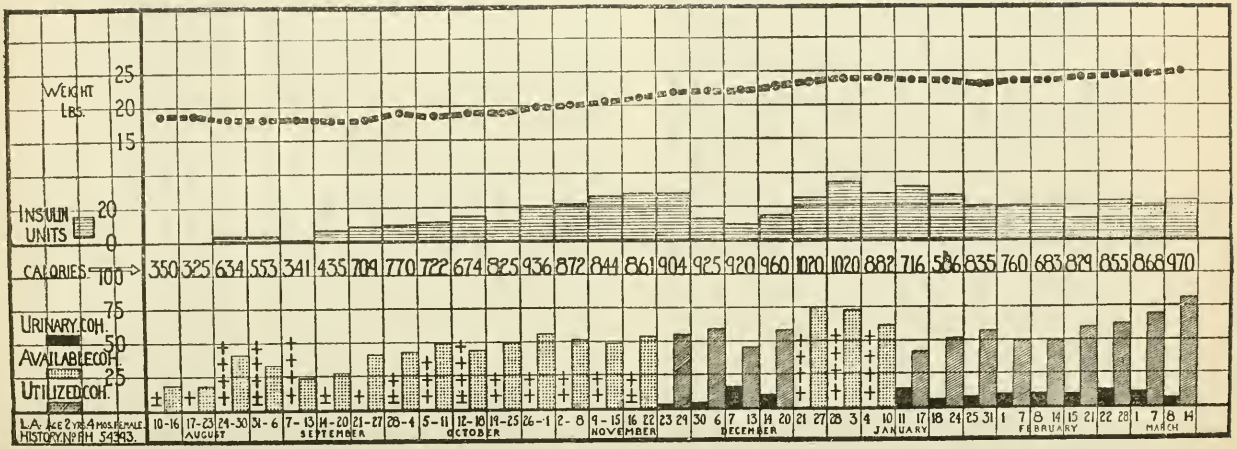
CASE HISTORIES.

Case 1. L. A. Age. 2 years.* Presbyterian Hospital History No. 54393. Date of onset (by symptom and urine analysis) about June 1, 1922, at age of 1 year, 7 months. Followed since June 14, 1922.

History and Summary of Pre-Insulin Course: No diabetes in family. Patient was a healthy baby, whose weaning at 3 months was attended with much gastro-intestinal disturbance until a Dryco diet was given, on which the child did well and seemed to develop normally. At the age of 3 to 4 months she had an abscess on the buttock. The urine was then tested for sugar, but was found negative. At one year of age, she had bilateral purulent otitis, and on this occasion also the urine was found sugar free. At 1 year, 7 months, she had another abscess on the buttock, became fretful and irritable, and lost rapidly in weight and strength. She stopped walking and talking; her hair came out; dentition was arrested. No abnormal appetite, thirst, or urination was observed. Shortly after this the urine was found to contain sugar. She was brought 2 weeks after the onset of the symptoms to the Presbyterian Hospital, where she was treated for a month.

On admission she weighed 22.4 pounds, and appeared pasty, pale, and slightly edematous. Blood sugar was 0.244 per cent., blood CO_2, 30.6 volumes per cent. In ten days on carbohydrate, 25 gm., protein, 30 gm., fat, 30 gm., urine showed 2 to 3 per cent. sugar, but blood sugar fell to

* The age given for each case is that for the calendar year during which insulin therapy was started.


WEIGHT LBS.
25
20
15
INSULIN UNITS
20
0
CALORIES
100
350 325 634 553 341 435 709 770 722 674 825 936 872 844 861 904 925 920 960 1020 1020 882 716 586 835 760 683 809 855 868 970
75
URINARY COH.
50
AVAILABLE COH.
25
UTILIZED COH.
L.A. AGE 2 YRS 4 MOS FEMALE
HISTORY NO 84 54983.
10-16 17-23 24-30 31-6 7-13 14-20 21-27 28-4 5-11 12-18 19-25 26-1 2-8 9-15 16 22 23 29 30 6 7 13 14 20 21 27 28 3 4 10 11 17 18 24 25 31 1 7 8 14 15 21 22 28 1 7 8 14
AUGUST
SEPTEMBER
OCTOBER
NOVEMBER
DECEMBER
JANUARY
FEBRUARY
MARCH

Case I

0.098 per cent. and blood CO_2 rose to 48.5 volumes per cent. On the fourth day of carbohydrate, 5 gm., protein, 15 gm., fat, 15 gm., urinary sugar disappeared. This diet was the highest on which (before insulin treatment) she could be kept continuously sugar free, though for two periods of four and six days she tolerated carbohydrate, 10 gm, protein, 20 gm., fat, 35 gm. Three months after onset she weighed 18.7 pounds, with considerable edema of legs and feet. Average diet for last week before insulin administration was carbohydrate, 7 gm., protein, 20 gm., fet, 24 gm., on which the urine constantly showed traces of sugar and acetone. The outstanding features in this case during the period of observation (June 14, 1922 to August 16, 1922) were: (1) an extremely low food tolerance, and (2) an unusual tendency to develop acidosis.

Course under Insulin Therapy: Chart shows steady increase in weight and carbohydrate utilization coincident with insulin therapy. In this case, as time goes on, it would seem that smaller doses of insulin are required to utilize a given amount of carbohydrate. The diet in the last three weeks of the chart was carbohydrate, 55 gm., protein, 40 gm., fat, 55 gm.

Abscesses at site of injection: Between January 7 and January 26, five abscesses on the buttocks were opened.

Independent infections.—On February fifth, child had a temperature of 104° for five or six hours; since then she has frequently shown slight rises of temperature (about one degree) possibly due to a low-grade cystitis.

Serum sickness: September sixth to eight, urticaria and edema.

Insulin shock: None.

Case II. A. B. Age 9 years. History No. 945-G. Date of onset: (1) By symptoms—January, 1921. (2) By urine analysis—March,1921.

Followed since April, 1921.

History and Summary of Pre-Insulin Course: No diabetes in family. Patient's health and development were normal, except for unusual nervousness, up to age of seven. She had a severe gastro-intestinal upset with some loss of weight in the summer of 1920, but in the fall regained weight up to a maximum of 49½ pounds. In January 1921, it was noticed that she was getting thinner, although her appetite was unusually good; and at the end of that month she began rather suddenly to drink and excrete large amounts of fluid, often wetting the bed at night or being incontinent in the daytime. A casual specimen then examined was reported sugar-free. In February she had lost 3 pounds (to 46½), but the urine again showed no sugar. In March, however, sugar was discovered in the urine and dieting was begun. Weight was then 42¾ pounds, and for the next one and one-half years remained between 40 and 42. In April, patient was sugar-free on diet of carbohydrate, 38 gm., protein, 45 gm., fat, 65 gm., with a blood sugar of 0.119 per cent. She maintained approximately this same food tolerance till November 1921, when she began to

WEIGHT Lbs.
60
55
50
45
40
INSULIN UNITS
40
20
0
CALORIES
AVAILABLE COH
URINARY COH
UTILIZED COH
125
100
75
50
25
0
AUGUST
SEPTEMBER
OCTOBER
NOVEMBER
DECEMBER
JANUARY
FEBRUARY
MARCH

show occasional traces of sugar on carbohydrate, 35 gm., protein, 40 gm., fat, 65 gm. In December, a severe cold brought out more sugar, but after two fast days diet was gradually raised again to carbohydrate, 30 gm., protein, 50 gm., fat, 80 gm. During the following spring the child was thin, hungry, and irritable. In April 1922, tolerance had fallen to carbohydrate, 25 gm., protein, 40 gm., fat, 50 gm., with a blood sugar of 0.163 per cent. and blood CO_2 of 46.6 volumes per cent. In July she was taking carbohydrate, 25 gm., protein, 50 gm., fat, 80 gm., but by the end of August she occasionally showed sugar on diets as low as carbohydrate, 15 gm., protein, 45 gm., fat, 85 gm. In the last week before the beginning of insulin therapy, food was carbohydrate, 12.5 gm., protein, 35 gm., fat, 70 gm., (825 calories), yielding available carbohydrate of 33.2 gm. (calculated from food only, as urinary nitrogen was not determined); urine during this period showed only an occasional trace of sugar. Weight was 40⅛ pounds. Insulin was started August 30, 1922.

Course under Insulin Therapy: Chart shows steady gain in carbohydrate utilization and weight coincident with insulin administration. In this case again, it seems that the dosage of insulin required for the utilization of a given amount of carbohydrate gradually becomes somewhat smaller. From March 1922 to November 1922, patient gained 1¼ inches in height; from November 1922 to March 1923, she gained ½ inch. Distribution in diet of carbohydrate, protein and fat in last five weeks on chart was carbohydrate, 120 gm., protein, 70 gm., fat, 125 gm.

Abscesses at site of injection: None.

Independent infections: End of November 1922, slight cold. December 25, 1922, rather severe cold with earache.

Serum sickness: Slight symptoms lasting for a few hours on one day (September 4, 1922).

Insulin shock: Severe shock, with epileptiform convulsions, on November 27, 1922. Mild shock, February 6, 1923.

Case III. R. A. Age 9 years. Presbyterian Hospital History No. 41902. Date of onset: (1) By symptoms—February, 1919. (2) By urine analysis—March, 1919. Followed since March 2, 1919.

History and Summary of Pre-Insulin Course: No diabetes in family. Child had been in good health up to February 1919, when he began to drink a great deal of water and to wet the bed at night. Sugar was found in the urine in March. He was admitted to the hospital May 7 for six days, during which time the urine was sugar-free, the blood sugar normal. During the remainder of 1919 he did very well, being free from urinary sugar on a diet as high as carbohydrate, 85. gm., protein, 90 gm., fat, 120 gm. His weight increased from 42.5 pounds in May to 49 pounds in December.

In the first part of 1920 he did well, but in April, following an acute respiratory infection his tolerance fell markedly. A period of greatly lowered diet with fast days enabled him to be sugar-free on carbohydrate,

40 gm., protein, 90 gm., fat, 80 gm., in the latter part of May 1920. The tolerance did not materially improve, and during the remainder of this year he continually showed sugar on a diet of carbohydrate, 50 gm., protein, 95 gm., fat, 70 gm., becoming sugar-free when half day diets were taken. On December 6, 1920, he weighed 48½ pounds.

During January 1921, he was noted as appearing physically in excellent condition. Early in February he had measles and his food tolerance became considerably lower. During April and May he did very badly and was admitted to the hospital from May 26 to June 17. He left sugar-free on a diet of carbohydrate, 20 gm., protein, 50, gm., fat, 60 gm., weighing 45¾ pounds. On this diet he remained sugar-free for three weeks, but then again showed sugar. During September he was kept sugar-free on carbohydrate, 15 gm., protein, 50 gm., fat, 80, gm., with a weekly half-day, and on October 11 he weighed 45¼ pounds. He then began anew to show sugar and did badly until on November 25 he was admitted to the hospital. At this time there was a mild degree of acidosis, blood CO_2 being 28.1 volumes per cent. and blood sugar 0.271 per cent. On December 21 he was discharged on a diet of carbohydrate 10 gm., protein, 25 gm., fat, 40 gm., with urine sugar-free and blood sugar 0.139 per cent. Weight 44½ pounds.

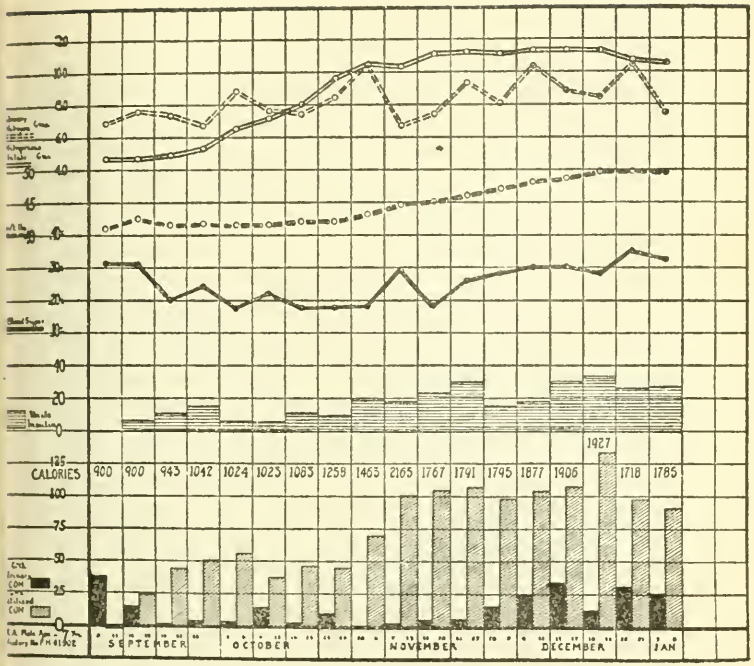
During January and February 1922, his tolerance appears to have been exceedingly low and he continually showed sugar on a diet of carbohydrate, 10 gm., protein, 20 gm., fat, 60 gm. He was readmitted to the hospital on March 28 with a marked degree of acidosis, with a blood CO_2 of 13.7 volumes per cent. and blood sugar of 0.306 per cent, acetone and diacetic of urine ++++. He weighed 39.4 pounds on admission. He was discharged on April 29 with a blood sugar of 0.168 per cent., weight 39 pounds, sugar-free on a diet of carbohydrate, 10 gm., protein, 30 gm., fat, 50 gm. During the summer he showed sugar on this diet, being cleared up on half days, but showing no improvement in tolerance. He was admitted to the hospital for the fourth time on September 2 for insulin treatment.

During a preliminary eight days in the hospital without insulin he averaged 34.3 gm. urinary glucose on diet of carbohydrate, 10 gm., protein, 30 gm., fat, 80 gm. (908 calories), with average daily nitrogen loss of 3.47 gm. Available carbohydrate was 36.7 gm., and utilized carbohydrate only 2.4 gm. per day. Blood sugar averaged 0.310 per cent., blood CO_2 40.9 volumes per cent. Weight 41 to 42 pounds.

Course under Insulin Therapy: Chart shows steady increase in utilized carbohydrate and weight coincident and parallel with insulin dosage. Positive nitrogen balance is early established. Between October 1922 and March 1923 patient increased about 3 cm. in height. Distribution in diet of carbohydrate, protein and fat in last two months of chart was protein, 70 gm., fat, 130 gm., with carbohydrate varying from 65 gm. to 105 gm.

Abscesses at site of injection: None.

Independent infections: None.



Case III

Serum sickness: Urticaria and some edema, September 26 to 28; October 4 to 11; October 26. Skin test showed sensitiveness to lot of insulin then in use, and patient was desensitized by Dr. Mackenzie. Skin tests with subsequent lots of insulin gave only slight reaction.

Insulin shock: Of varying but always mild degree of severity, November 5, 6, 7, 25; December 2, 3, 6, 8, 20, 21, 22.

Case IV. E. M. M. Age. 15 years. Presbyterian Hospital History Number 50830. Date of onset: (1) By symptoms—September 1918. (2) By urine analysis—October 1918. Followed since November 1, 1918.

History and Summary of Pre-Insulin Course: No diabetes in family. Child was very fond of sweets, ate many potatoes and much sugar. She had been in excellent health up to the age of ten, when suddenly within three days she became peevish and developed polyphagia, polydipsia, polyuria, and pruritus. Her weight fell from 63 or 64 pounds (2 months

before onset) to 60 pounds (one week after onset) to 57 pounds (8 weeks after onset).

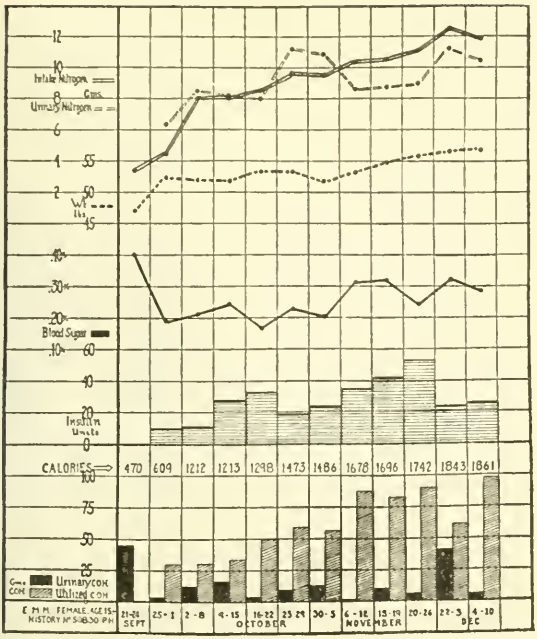
She was first seen eight weeks after onset. Glycosuria had been discovered two weeks before and her carbohydrates limited since then. At this time she appeared emaciated and had dry scaly skin and slight edema of the feet. Breath had no acetone odor. Urine showed ++ sugar. She was put on three 2 egg days, after which glycosuria disappeared. During the next year her diet was gradually raised to carbohydrate, 90 gm., protein, 95 gm., fat, 130 gm., with an occasional partial fast day. She rarely showed even a faint trace of sugar in the urine, remaining sugar-free for as many as 65 days at a time. She returned to school and gained weight, reaching 66 pounds in November 1919.

About this time her tolerance began to decrease, more frequent half days were needed to keep her sugar-free, and an attack of influenza in January 1920, reduced her tolerance further. She began to lose weight. She was kept sugar-free in May on carbohydrate, 50 gm., protein, 100 gm., fat, 120 gm., but showed occasional subjective symptoms of acidosis. By January 1921, she was showing sugar constantly on carbohydrate, 45 gm., protein, 90 gm., fat, 90 gm., but could be kept sugar-free on carbohydrate, 35 gm., protein, 70 gm., fat, 70 gm. In the next six months she went steadily down hill. In July 1921, she was admitted to the hospital showing sugar on carbohydrate, 20 gm., protein, 50 gm., fat, 100 gm. Blood sugar was 0.224 per cent., blood CO_2 38 volumes per cent, weight 52.5 pounds, basal metabolism plus 6 per cent. Her glycosuria cleared on two 2 egg days and she was sent out after two weeks on carbohydrate, 10 gm., protein, 40 gm., fat 50 gm. In the next year her clinical condition grew much worse. She could not return to school, because of progressive weakness. She showed a constant glycosuria on a diet varying between carbohydrate, 10 gm., protein, 25 gm., fat, 55 gm., and carbohydrate 10 gm., protein, 30 gm., fat, 90 gm. with occasional symptoms of acidosis.

She was admitted to the hospital again in June 1922, in acidosis, with 40 to 55 gm. of sugar in the 24 hour urine specimen. With 5 days of complete fasting and two 3 egg days urine sugar fell to 14 gm., but never cleared. Blood sugar at this time was 0.428 per cent., blood CO_2 on admission 15 volumes per cent., weight 46¾ pounds. Symptoms of acidosis were relieved, and she was sent out on carbohydrate, 6 gm., protein, 25 gm., fat, 30 gm., on which she showed between 1 and 2 per cent. sugar until her third admission on September 21, 1922, for insulin treatment.

On three control days before insulin was started, this child, on a diet of carbohydrate, 10 gm., protein, 25 gm., fat, 40 gm. (520 calories), excreted an average of 43.8 gm. sugar or 19.3 gm. more carbohydrate than was afforded by her food. Urinary nitrogen was not determined. She weighed 48 pounds with edema, blood sugar was 0.425 per cent; blood CO_2 35.3 volumes per cent; basal metabolism —26 per cent.

Course under Insulin Therapy: Chart shows steady increase in weight and utilized carbohydrate, coincident with insulin therapy. Nitrogen belance is established. The amounts of insulin required for utilization of a given amount of carbohydrate seem, in this case, as treatment goes on,



Case IV

to become slightly smaller. Between October 1922, and March 1923, patient gained about 3.2 cm. in height. During period on chart, food protein was gradually increased from 50 gm. to 75 gm., fat, from 40 gm. to 140 gm., carbohydrate from 10 gm. to 55 gm. Diet in last week was carbohydrate, 55 gm., protein, 75, fat, 140. (1840 calories).

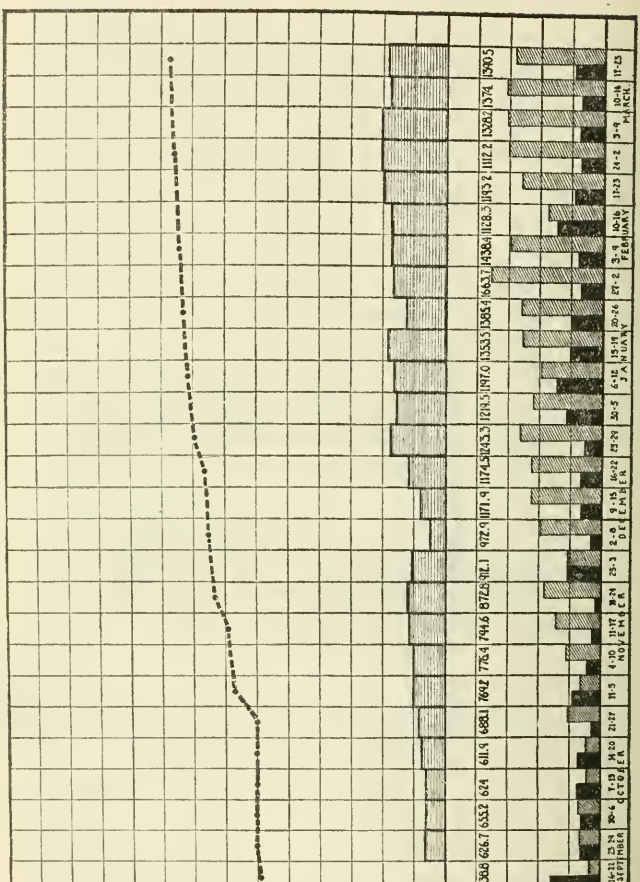
Abscesses at site of injection: None, during period covered by chart. She later developed several small ones.

Independent infections: Slight cold, October 30 to November 1.

Serum sickness. None.

Insulin shock: Mild symptoms on November 6, 26 and 27.

Case V. D. D. Age 6 years. History No. 794-G. Date of onset: (1) By symptoms—May 1919, to October 1919. (2) By urine analysis—February 1920. Followed since September 6, 1922.


Weight Lbs.
45
40
35
30
Insulin units
40
20
0
100
CALORIES
75
50
25
0
Urine gm. sugar
Urine gm. acetone
Blood sugar mg.
14-21 23-28 SEPTEMBER
30-4 7-13 OCTOBER
18-20 21-27
11-3
4-10 11-17 18-24 NOVEMBER
25-1 2-8 9-15 16-22 23-29 30-5 DECEMBER
6-12 13-19 20-26 27-2 JANUARY
3-9 10-16 FEBRUARY
10-16 17-23 MARCH
5368 626.7 6552 624 611.9 688.1 769.2 778.4 794.6 872.8 912.1 972.9 1071.9 1174.5 1243.5 1219.5 1197.0 1353.5 1385.4 1463.7 1438.4 1428.5 1483.2 1112.2 1328.1 1374 1390.5

Case V

History and Summary of Pre-Insulin Course: Great-grandfather a diabetic. Nutrition and health good, except for pneumonia and otitis at the age of one, up to appearance at age of 3, of a transitory pruritus vulvae. Five months later, thirst, polyuria with frequency and burning, polyphagia and loss in weight, strength and nervous stability were observed. These progressed for 4 months up to a severe attack of acidosis, during which glycosuria was first discovered. Weight at this time was 18 pounds, a drop of 22 pounds from maximum of 40 pounds. Following two short starvation periods, glycosuria and ketonuria cleared, and a tolerance of 50 gm. carbohydrate was gradually established, and maintained for about six months, with reacquisition of previous maximum weight of 40 pounds. At the end of the year, however, carbohydrate tolerance had dropped to 30 gm., and in three months more to 20 gm., with falling weight. Near the end of two years of treatment, tolerance was carbohydrate, 14 gm., protein, 28 gm., fat, 39 gm., and soon after this the tolerance was carbohydrate, 10 gm., protein, 28 gm., fat, 39 gm. For four months before insulin was started (September 1922), all efforts to check glycosuria were unsuccessful. On all diets tried, urine constantly showed sugar. Weakness was such that she was dyspneic on exertion and unable to stand alone. Fluid intake and output were not at this time excessive and irritability was less. When first seen by us in September 1922, she weighed 29¼ pounds; physical examination was negative except for emaciation, weakness, and full protuberant abdomen. On a diet of carbohydrate, 10 gm., protein, 12 gm., fat, 23 gm. (304 calories), the urine showed a trace of sugar and ketone bodies.

Course under Insulin Therapy: Chart shows gradual increase in weight and utilized carbohydrate coincident with insulin therapy. Her true weight when she was first seen must have been considerably lower than that given on the chart, but was masked by an unusual degree of edema. The increasing amounts of utilized carbohydrate correspond in general to the amounts of insulin given, with, in this case, a slight relative increase in the utilized carbohydrate. The food carbohydrate was raised from 12 gm. to 55 gm., protein from 33 gm. to 70 gm., fat from 40 gm. to 100 gm.

Abscesses at site of injection: None.

Independent infections: Discharging ear, February 12 to March 19. Severe cold, February 8.

Serum sickness: None.

Insulin shock. None.

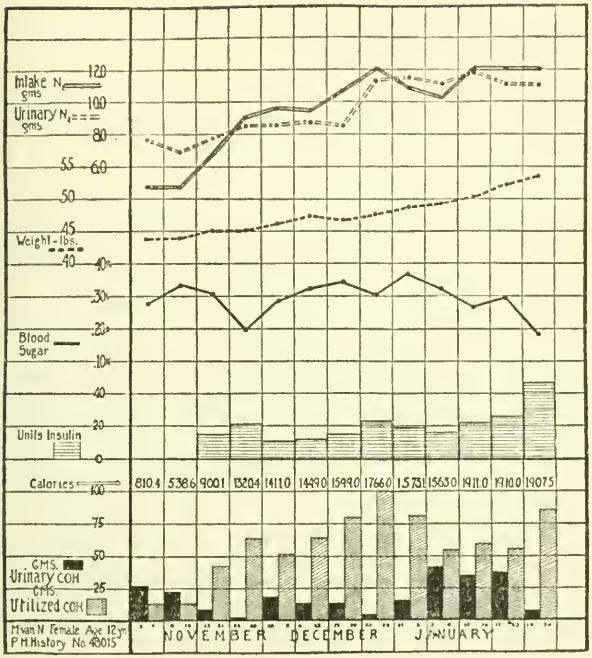
Case VI. M. V. N. Age 12 years. Presbyterian Hospital History No. 48015. Date of onset: (1) By symptoms—October 24, 1920. (2) By urine analysis—November 5, 1920. Followed since November 8, 1920.

History and Summary of Pre-Insulin Course: Grandmother a diabetic. Patient was a normal, healthy child, whose best weight at 12 years was 57½ pounds. Onset of diabetes was sudden, two weeks before her ad-

mission to the hospital. Polyuria was first noted, two days later polydipsia and polyphagia began. She lost four pounds in two weeks. Glycosuria was discovered, three days before admission, by a local doctor, who put her on a diet high in fat and low in carbohydrate. On the second day of thia diet she became drowsy, was nauseated, and vomited. On admision she was drowsy, but could be roused. Cheeks were flushed, lips very red, tongue dry, eyeballs soft, heart rapid, breathing very deep with acetone odor to breath. Examination was otherwise negative. She weighed 53.5 pounds. Her fluids were forced to 3000 cc. per day. She was given sodium bicarbonate, 26 gm., and put on a diet of carbohydrate, 70 gm., protein, 30 gm., fat, 0 gm. for 3 days. Blood CO_2 rose from 10.9 volumes per cent. to 57.6 volumes per cent. Blood sugar remained at 0.380 per cent. There was great clinical improvement. Urinary sugar disappeared after a day on carbohydrate, 30 gm., protein, 10 gm., fat, 0 gm. and one day on carbohydrate, 10 gm., protein, 10 gm., fat 0 gm. After one complete fast day, the diet was gradually raised to carbohydrate 80 gm., protein, 24 gm., fat, 10 gm., before sugar reappeared. She was discharged after one month, sugar-free on carbohydrate, 30 gm., protein, 50 gm., fat, 60 gm.

She was treated in the out-patient department, and was sugar-free for the next eight months, on a diet which was gradually raised to carbohydrate, 50 gm., protein, 65 gm., fat, 110 gm. Her weight rose to 56.5 pounds. Two blood sugars during this period were normal. Toward the end of this time (August 1921), her tolerance began to fall, until, one year after onset (November 1921), she showed sugar on carbohydrate, 20 gm., protein, 35 gm., fat, 35 gm., and was sugar-free on carbohydrate 10 gm., protein, 25 gm., fat, 25 gm. Acetone was always present in the urine from about this time on. In November 1921, she had a tooth extracted, which proved to have a pus sac at the root, and during the next few months she suffered from frequent colds. In the first six months of her second year she was kept on a gradually decreasing diet with frequent fast days, and was admitted to the hospital in May 1922, showing sugar on carbohydrate, 20 gm., protein, 20 gm., fat, 50 gm. Physical examination was negative, weight 46 pounds, blood sugar 0.298 per cent. On a diet of carbohydrate, 14 gm., protein, 20 gm., fat, 90 gm., her daily urinary glucose averaged 28 gm. Her carbohydrate was cut to 7 gm. with no effect on the glycosuria. She was then put on carbohydrate 0 gm., protein, 20 gm., fat, 20 gm., on which she became practically sugar-free after six days. She was kept on this for 14 days in all, and then remained sugar-free for 5 days on carbohydrate, 5 gm., protein, 20 gm., fat, 30 gm., but began to show sugar on carbohydrate, 5 gm., protein, 30 gm., fat, 35 gm., and continued to show a daily output of 20 to 30 gm. of sugar on carbohydrate, 6 gm., protein, 25 gm., fat, 50 gm. She was discharged on carbohydrate 5 gm., protein, 25 gm., fat, 60 gm., weighing 51.75 pounds, and in the next two months showed only a trace of sugar most of the time though her diet was raised to carbohydrate, 7 gm., protein, 30 gm., fat, 65 gm. It should be noted that her urinary volume during this time was very large.

Third admission October 31, 1922, for insulin therapy. During a control period of two weeks before insulin was started, daily urinary sugar aver-



Case VI

aged 25.6 gm. on a diet affording 39.15 gm. available carbohydrate, with average daily nitrogen loss of 2.6 gm. This made the utilized carbohydrate 13.6 gm. Blood sugar averaged 0.297 per cent. and blood CO_2 48.7 volumes per cent. Weight was constant at 44 pounds. Basal metabolism —38 per cent. Average urinary volume was 5,000 cc. with consequent great loss of heat. Clinical condition was characterized by extreme weakness and lethargy.

Course under Insulin Therapy: Chart shows increase in weight and carbohydrate utilization coincident with insulin therapy. Positive nitrogen balance is attained. The maximum insulin effect is seen at the end of the second month, and is followed by three weeks of relatively delayed progress, with return to negative nitrogen balance. The gain in weight was uninterrupted and was not accounted for by fluid retention. During this period, on account of shortages in supply, insulin therapy was several times interrupted for a day or two at a time. Over the period covered by

the chart gain in height was about 3 cm. Distribution in diet of carbohydrate, protein, and fat in last three weeks of chart was, carbohydrate, 50 gm., protein, 75 gm., fat, 150 gm.

Abscesses at site of injection: None.

Independent infections: January 22, acute pharyngitis and cervical adenitis. January 25, maxillary sinusitis; antrum opened, found to contain pus, and irrigated daily from January 25 to February 9.

Serum sickness: None.

Insulin shock: None.

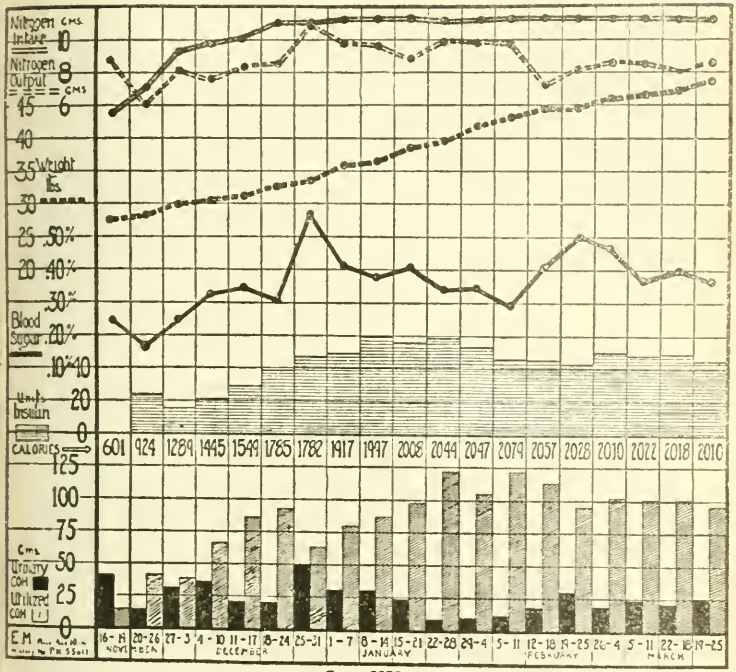
Case. VII. E. J. M. Age 10 years. Presbyterian Hospital History No. 55611. Date of onset: (1) By symptoms—February 22, 1918. (2) By urine analysis—March 1918. Followed since November 16, 1922.

History and Summary of Pre-Insulin Course: No diabetes in family. Past history irrelevant up to onset of diabetes 4½ years ago. First symptoms were polyuria and thirst, observed February 22, 1918. At that time he weighed 38 pounds. Sugar was found in March 1918; he was placed on two days' starvation and became sugar-free at once. During the subsequent 8 months, diet was increased and he gained 6 pounds in weight. In December 1919, following an attack of influenza, he began to show large amounts of sugar in the urine and lost weight rapidly, the glycosuria, however, being controlled fairly easily by diet and occasional fast days. The tolerance steadily diminished, and for the past one and one-half years he showed sugar constantly. During the last six months he grew very weak and was unable to go out walking as he had done before. Four months before admission to this hospital his parents were told that the case was hopeless, and after that he was given more food to satisfy his whims. His weakness progressed, and face and legs became edematous. On admission to the hospital, November 16, 1922, for insulin therapy, he was unable to lift his head from his pillow without help. Emaciation was extreme: at the age of ten years, he weighed only 27 pounds.

In a control period of three days before insulin was started, on diet of carbohydrate, 20 gm., protein, 35 gm., fat, 40 gm. (603 calories), daily excretion of sugar averaged 41.1 gm., and daily nitrogen loss 3.3 gm. Of 56 gm. available carbohydrate, he was able to utilize only 14.8 gm. Blood sugar was 0.240 per cent., blood CO_2 50 volumes per cent, basal metabolism —15 per cent.

Course under Insulin Therapy: Chart shows, coincident with insulin therapy, an immediate rise in carbohydrate utilization to a level which later roughly parallels the curve of insulin dosage. Positive nitrogen balance is at once attained, and the steady gain in weight is accompanied by considerable daily retention of nitrogen. From November 24, 1922, to April 2, 1923, gain in height was about 2 cm. The diet in the last two months of the chart was carbohydrate 80 gm., protein, 70 gm., fat, 150 gm.

Abscesses at site of injection: None.



Case VII

Independent infections: Mild upper respiratory infection, November 24 to 30.

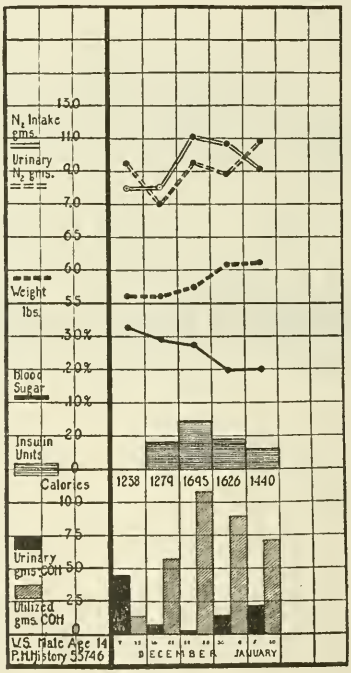
Serum sickness: None.

Insulin shock: Slight symptoms occurred very frequently: Dec. 1, 4, 5, 6, 7, 9, 14, 23, 29; January 15, 16, 19, 23, 25, 26, 28, 29; February 1, 3, 5, 11. March 10, 18. Moderately severe symptoms: January 14, February 7, 25.

Case VIII. W. S. Age 14 years. Presbyterian Hospital History No. 55745. Date of onset: April, 1915. Followed since December 6, 1922.

History and Summary of Pre-Insulin Course: Family and past history were irrelevant up to onset of diabetes eight years ago, following measles, with symptoms of loss of weight, polyuria, and polydipsia.

During the following years, under the care of a number of physicians, his condition appears to have been stationary. November, 1920, his weight was 64 pounds. In January, 1921, his diet was carbohydrate, 60 gm., protein, 75 gm., fat, 106 gm. In September, 1921, it had been reduced to carbohydrate, 25 gm., protein, 70 gm., fat, 122 gm., with one fast day each week. At that time he weighed 65 pounds (with clothes), and blood sugar was 0.153 per cent. During the past year, on a diet chiefly of vegetables and meat, there were periods when his urine was sugar-free. Four months before admission to this hospital, the dietary regime was completely broken down, and he ate candy and sweets in addition to his diet. Symptoms increased, and he had a siege of furunculosis. At no time in his course did he have symptoms of severe acidosis. On December 6, 1922, he was admitted to the hospital for insulin therapy.



Case VIII

In a five day control period before insulin was started, on diet of carbohydrate, 25 gm., protein, 50 gm., fat, 100 gm. (1238 calories), daily excretion of carbohydrate averaged 45.2 gm. and daily nitrogen loss 1.5 gm. Of 59 gm. available carbohydrate, he was able to utilize only 13.7 gm. Weight fell from 57½ pounds to 55½ pounds. Average blood sugar was 0.312 per cent., blood CO_2 38 volumes per cent., basal metabolism was plus 2 per cent.

Course under Insulin Therapy: Chart shows marked rise in utilized carbohydrate coincident with insulin therapy, and a corresponding decrease when the dose is diminished. Weight gradually rises, and positive nitrogen balance is attained. Distribution in diet of carbohydrate, protein, and fat in last week of chart was carbohydrate, 55 gm., protein, 60 gm., fat, 105 gm.

Abscesses at site of injection: None.

Independent infections: None.
Serum sickness: None.

Insulin shock: Slight symptoms, December 21.

Case IX. A. K. Age 14 years. Presbyterian Hospital History No. 55843. Date onset: (1) By symptoms, October, 1919. (2) By urine analysis, January, 1920. Followed intermittently since January, 1920.

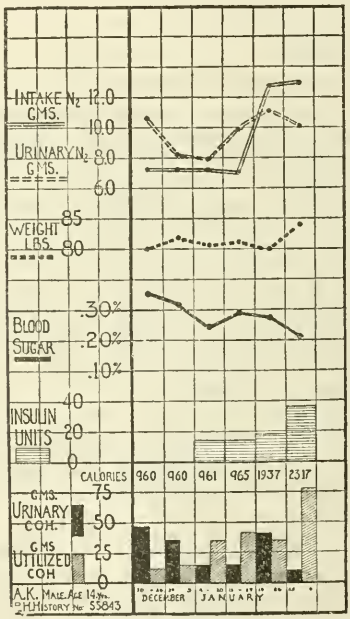
History and Summary of Pre-Insulin Course: Past history has no bearing on present disease except possibly for the fact that he had an unsually complete list of the various exanthemata. Up to three years ago his general health was good. Diabetes began in October, 1919, with polyuria, polydipsia, and polyphagia. Sugar was found in the urine in January, 1920, and he was then placed under the care of one of us (H. R. G.). The patient became sugar-free on a diet of carbohydrate, 30 gm., protein, 50 gm., fat, 50 gm., and this was increased during the following six months to carbohydrate, 60 gm., protein, 90 gm., fat, 130 gm. He did very well, his symptoms largely vanished, and he gained in weight from 87 pounds to 94 pounds.

The diet was then not well kept and a severe rhinitis further reduced his tolerance. In October, 1920, he went to a private sanatorium. During the three weeks of his stay he was on an extremely low diet, and lost weight, but became sugar-free, with normal blood sugar. After three months at home, during which time his diet was very poorly kept, he returned to the sanatorium in January, 1921. There he was placed on practical starvation; he deserted at the end of one week.

From then until shortly before admission to this hospital, he was not on a measured diet, and weighed at times as much as 102 pounds. But further infections reduced his tolerance, and in September, 1922, he had considerable edema, and acetone bodies in the urine. For three weeks in October under strict observation at another hospital, he could not be rendered sugar-free on a diet affording only 700 calories. He returned to New York in November and was placed on a diet of carbohydrate, 25 gm., protein, 15 gm., fat, 80 gm., for three weeks, and then on carbo-

hydrate, 20 gm., protein, 45 gm., fat, 75 gm. All this time he continued to show sugar and just prior to admission excreted as much as 100 to 150 gm. per day. On December 19, 1922, he was admitted to this hospital for insulin therapy.

During a control period of two weeks without insulin, he averaged 37.9 gm. urinary glucose on a diet of carbohydrate, 20 gm., protein, 45 gm., fat, 75 gm., with average daily nitrogen loss of 1.38 gms. Available carbohydrate was 50.8 gm. and utilized carbohydrate 12.9 gm. per day. Blood sugar was 0.352 per cent., blood CO_2 36.6 volumes per cent., basal metabolism on admission —6 per cent., one month later —30 per cent. Admission weight of 86 pounds included a great deal of edema. It dropped in four days to 75½ pounds, then gradually rose during control period to 81½ pounds.



Case IX

Course under Insulin Therapy: Chart shows marked increase of utilized carbohydrate with insulin administration. Weight was about constant and nitrogen balance negative during most of this short period of treat-

ment. However, during the next four and a half months after the period covered by the chart, he has gained 20 pounds.

Abscesses at site of injection: None.

Independent infections: None.

Serum sickness: None.

Insulin shock: None.

Discussion.

In the cases here presented, and in some thirty odd additional cases which will form the basis of a subsequent report, we have as yet met with no therapeutic failures. In the group of cases discussed above, definite and continuous gain in weight is seen. These gains in weight vary considerably according to the length of time the patients have been under treatment, the age and original weight of the child, the amount of insulin and food given, and perhaps the specific constitution of the individual. The gain in weight ranges from only two pounds in three months to twenty-two pounds in seven months. Simultaneously, there has been a corresponding increase in muscular strength and vigor, and great improvement in the patients' sense of mental and physical well-being. The gain in carbohydrate tolerance and in total food tolerance has also been striking in all instances, and it has seemed to vary somewhat in accordance with the amount of insulin given and the original severity of the diabetes.

Glycosuria has purposely never been totally abolished for any consecutive period longer than ten days. Other observers, (personal communications), however, have insisted upon a sugar-free urine, and have accomplished this; but we have chosen to allow a moderate glycosuria in all cases, as this procedure has proved in our hands to be the most practical method of lessening the possibility of insulin over-dosage—with its disagreeable and sometimes alarming symptoms. In the earlier stages of this work, together with other observers, we were making an effort to maintain a consistently sugar-free urine, with the result that relatively frequent and sometimes severe symptoms of insulin over-dosage were met with. These effects have occurred much less frequently since the cases have been allowed to show a moderate amount of sugar in the urine daily. When the carbohydrate of the food was high, i.e., 80 to 120 gm. per day, we have tried to keep this amount below 20 gm. per day. With lower carbohydrate intakes,

the desired quantity of sugar in the urine has been 10 gm. or less per day. In only one case (Case VII) has there been any evidence of insulin over-dosage since this plan was adopted, and in this case the over-dosage effects have always been mild.

The blood sugar observations as recorded on the charts require explanation. All these blood sugars were taken fasting at 8 a. m., at least 15 hours after the last dose of insulin. Two-hourly blood sugars taken on a few cases over a period of eight hours have demonstrated that eight hours was the maximum period during which insulin was effective in lowering blood sugar. One would, therefore, expect to find the highest blood sugar values of the 24 hour period at 8 a.m., this being the hour farthest removed from the last dose of insulin. The fact that the early morning blood sugar values of our patients remained high during insulin therapy is in accordance with these observations.

One of the most striking and constantly observed effects of insulin in this group of diabetic children has been the rapid and complete disappearance of ketone bodies from the urine. When the initial ketosis was moderate in degree and accompanied by little or no evidence of an acidosis, the urine was occasionally found to be free from diacetic acid within 48 hours after the initiation of insulin therapy. In every case, the amount of diacetic acid in the urine was markedly diminished after the first week of insulin therapy, and in only one case (Case II) did it persist for more than two weeks.

Case II showed faint traces of diacetic acid for the first eight weeks of daily insulin therapy.

At the start it was realized that one of the most important objects to be achieved for these extremely under-nourished children was restoration of weight and strength in as short a time as possible. This could be accomplished only by raising the diet as rapidly and as high as possible. In order to obtain this object, most of the cases were immediately put on a caloric intake two to three times as great as that on which they had previously been able to keep sugar-free. Naturally, the daily amount of insulin given was much greater than that which would have been necessary to bring about more gradual gain of weight on a lower diet. Taking the original pre-insulin food tolerance as our standard, we outlined our "insulin diet" roughly as follows: protein, 2 to 3.5 gm. per kilo body weight; carbohydrate, equal to, or 50 per cent. greater than the protein; fat sufficient to yield a total caloric

intake approximately 50 per cent. more than the theoretical basal reguirements of normal children with the same surface area and age. We realize that the same total caloric intake could have been attained with lower amounts of carbohydrate and protein and larger amounts of fat, and yet have kept the ketogenic-antiketogenic ratio of Zeller not higher than 3 to 1. Such a procedure, of course, would have required less insulin, but on the other hand it would have meant a return to the principles of former diabetic therapy: i.e., low carbohydrate—high fat diets,—which method we hoped insulin would enable us to avoid. In other words, what we have attempted to do is to make the diet as nearly normal in the quantitative relationships of carbohydrate, protein, and fat as the severity of the diabetes and our supply of insulin would permit.

At first we had no idea as to how much insulin was necessary to offset glycosuria on a given carbohydrate intake. Our usual procedure was to give five units of insulin once a day, before either the breakfast or noon meal, noting the effect of this dose on the sugar content of subsequent single urine voidings, and upon the total glycosuria of the corresponding 24 hour period. The insulin was then gradually raised at the rate of two to ten units daily until the urine was sugar-free. Later on in the course of the work, as we encountered instances of insulin over-dosage, we did not attempt to render the urine sugar-free, but chose instead to reduce glycosuria to a minimum and relatively constant quantity.

After the daily increases in insulin had reached the point where glycosuria was absent or sufficiently reduced, as noted above, the carbohydrate of the food was increased at the rate of 10 to 20 gm. every five or six days, up to the maximum carbohydrate level permitted by the supply of insulin at our disposal. Coincident with these increases in carbohydrate, insulin was again added (2 to 10 units at a time) as required to maintain a low and constant amount of sugar in the urine. We have as yet found no evidence that the degree of carbohydrate tolerance which any case of diabetes can achieve with insulin is limited by anything except the amount of insulin which can be given.

In these patients we stopped increasing the carbohydrate and caloric intake when the following requirements had been fulfilled: (1) a diet satisfying the patient's appetite, (2) continuous gain in weight and height, and (3) well-established positive nitrogen balance.

The high protein content of all the diets given to these children during insulin treatment seemed justifiable in view of their undernourished condition. The amount of protein given varied from 3 to 4 gm. per kilo body weight. All the patients took this well, without digestive disturbances. That they were able to use this amount of nitrogen was shown by the large positive nitrogen balances attained, sometimes amounting to 7 gm. per day. It may be that this high protein feeding accounted in some measure for the rapid rate of growth and gain in weight.

Serum sickness as noted above occurred in only three of the nine cases: Case II showed this phenomenon in very mild form and then only for one day; Case I showed serum sickness for two days in rather severe form; while Case III had urticaria with itching and edema of the entire body surface. An attempt was made with Case I to omit insulin for two days, reducing the diet, in order to alleviate the urticaria; this resulted, however, in the development of symptoms of severe acidosis. It was necessary to desensitize both patients I and III with small doses of insulin repeated at frequent intervals. The technique of this procedure was outlined by Dr. Mackenzie, and proved successful, as the patients have subsequently been able to continue on daily doses of insulin with no further urticaria.

Until November 1, 1922, the protein content of Iletin (Lilly) was relatively higher than that of subsequent lots used. In spite of this, no abscess formation was observed in any of the nine cases prior to January, 1923. At this time we were informed that the acidity of Iletin (Lilly) was greater than usual. This fact may account for the abscesses observed in Cases I and IV which occurred at or after this time. Case I had a total of five rather small abscesses at the sites of injection, extending over a period of three weeks (January 7 to January 26). These abscesses produced slight rises in temperature, but healed promptly after they had been opened. Case IV also developed abscesses at the site of injection which behaved in the same general way as those in Case I.

Alarming symptoms of insulin over-dosage, or "insulin shock." with the possibility of fatal results, make it important to emphasize this drawback to insulin therapy in diabetes. The early symptoms of "insulin shock," as we have observed them, are: weakness, dizziness, languor, epigastric distress or pain, sometimes faintness. These symptoms, if untreated, are followed

within a very short time (two to twenty minutes) by uneasiness of mind, extreme muscular weakness, slight tremor, profuse sweating, and sometimes hallucinations. These symptoms in turn are replaced by further more severe ones, such as muscular twitchings, unconsciousness, and finally epileptiform convulsions, which may be of great severity.

Summary

In a series of nine children suffering from severe diabetes, treatment with insulin has been followed by certain definite results: (1) arrest of the downward course of the disease; (2) achievement of a total food intake approximating the normal age requirement in calories; (3) steady gain in weight and growth, with increase in mental and physical vigor; (4) absence of severe or permanent ill effects.

Since these results have been observed over periods of only three to eight months, conclusions as to the continued beneficial effect of insulin over a period of years are not warranted.

Conclusion

Insulin, administered under carefully controlled conditions, has proved a safe and remarkably effective therapeutic agent in the treatment of severe juvenile diabetes.

THE CLINICAL USE OF INSULIN.

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Between June, 1922, and April, 1923, insulin was employed interruptedly or continuously in the course of treatment of some 150 diabetic patients. This report presents in brief the results obtained and comments that seem to have been warranted.

Material: The preparation of insulin was begun in this laboratory in June under the direct management of Dr. E. J. Witzemann. The method was essentially that developed by Collip and placed at our disposal through the courtesy of the Toronto group. A portion of the insulin used later was supplied by the Eli Lilly Company, and later still all of the material came from that source.

Route of Administration: Experiments were conducted with oral, rectal, vaginal, intranasal, intravenous, and subcutaneous administrations. Inunctions were also tried. Many variations were attempted in connection with each. Positive effects were obtained with subcutaneous and intravenous injections, very weak, doubtful or frankly negative results with the others. For practical clinical purposes subcutaneous injections were used to the exclusion of other modes of administration.

Technique of Hypodermic Injection and the Number and Time of Doses: Multiple doses have been largely eliminated and as a routine the single morning injection has been adopted for over 90 per cent. of all cases. It still happens occasionally that a case will be given 2 doses per day, one before breakfast and a smaller dose before the evening meal. Patients admitted in emergencies have been given insulin in divided doses to meet rapidly changing initial conditions. Finally all such cases have been reduced to one or two doses. The morning dose is given 30 minutes to 1 hour before breakfast. A few receive the dose 1 hour and 15 minutes before breakfast. These are cases which tend to show glycosuria after breakfast and an insulin reaction before the noon meal. With these it has seemed desirable to permit time for the insulin to absorb and thus secure a better registration of the insulin

action curve with the curve of glucose supply that follows the meal.

Preference has been given to insulin preparations containing at least 20 rabbit units per c.c. of volume. More concentrated preparations (e.g. 30 units per c.c.) have been used in some cases to reduce the volume of the injection and prolong the action curve. At present 20 units per c.c. is the strength employed by preference in the routine practice.

We have preferred 27 to 29 gauge hypodermic needles ¾ to 1 inch in length with 1½ to 2 c.c. glass syringes. The needles are inserted full length *under* the skin into a loose space. Pressure during injection is fastidiously avoided. The solution is warmed before injection. A flexor or adductor surface where the skin is thin and elastic and the subcutaneous space commodious is preferred. Care is taken to avoid raising a lump or welt at any time during injection. The needle point should be freely movable under the skin and the skin freely movable over the point of the needle. If it lies *in* the skin or in the firmer tissues beneath, pressures may arise during injection with unnecessary pain, soreness, scarring, necrosis, etc. Patients are taught to give their own injections whenever feasible. The thigh is then usually selected. If resistance is met the needle is readjusted until the fluid flows in with no more than the gentlest pressure of a finger tip on the plunger.

Method of Beginning and Advancing the Insulin Dosage: Various methods have been employed in the effort to find the most direct and expeditious. A number of preliminary plans were discarded after trial. Different cases present different problems and no one stereotyped procedure has proved equally effective in all. When a new case presents for management, the history and the first inspection and examination of the case permit one to judge of the type and degree of the diabetes and these determine the initial procedure. For illustration, assume that the patient is a young man of 30, that he looks emaciated and has the peculiar translucent pallor suggestive of a severe diabetes. He states that he has had the disease to his knowledge for only one year, that a year ago he weighed 160 lb. Now he weighs 110 lb. The disease has disabled him in a year. Unless the emaciation is attributable to enforced undernutrition such a case is obviously one of inherently severe diabetes. By diet adjustment alone nothing short of rigid restriction promises to restore him

to the non-diabetic status. In such a case there would seem to be no object in temporizing with intermediate diets. He is placed at once on a simple measured ration containing 0.5 to 0.8 gm. protein and 2.0 to 2.5 gm. fat per kg. of body weight plus the least amount of carbohydrate that can be given without making the diet unpalatable; for example:

	gm.	C. gm.	P. gm.	F. gm.	
Cream, 20 per cent.....	400	20	12	80	
Eggs	2		12	12	
Bacon	30		5	15	
Butter	20			17	
Total		20	29	124	Cal. 1312

At bed rest this suffices for caloric maintenance of the 50 kg. patient and commonly for a nitrogen balance. The glucose value of the diet estimated as C + .58 P + .1 F is 49 gm. On this diet either the urine becomes sugar-free or it does not. If it becomes sugar-free the diet is increased sufficiently to give it a glucose value some 25 im. higher, i.e. to 74 gm. or thereabouts. If this produces no gross glycosuria the diet is advanced again, and so on. Either on the initial diet or a later one there occurs a steady excretion of 15 to 25 gm. of glucose per day and one learns by the difference between the glucose supply and the glucose excretion the number of grams of glucose utilized per day, i.e. the existing tolerance "T" or the power to burn glucose. Having established a steady excretion of, say 10 to 25 grams of glucose per day, the probable dose of insulin necessary to check it can then be calculated. It has been our experience that 1 unit will account, directly, for 1.0 to 1.5 gm. of glucose. If this individual excretes steadily 25 gm. of glucose daily for 3 days, 20 units of insulin will approximately suffice to make the urine sugar "free." He then receives ½ of this calculated dose. First 1 drop of the preparation is injected intracutaneously as a sensitization test, and thirty minutes later the remainder of the 10 units (ordinarily ½cc.) subcutaneously. This is done as a rule in the afternoon and the 24 hours' urine closing the next morning usually shows a diminution of the glucosuria. In any event, barring the possibility that the initial 10 units causes an insulin or a protein reaction (rare) the patient receives 10 units of insulin before breakfast on the day after the initial test. The urine for that

day indicates the effect. On the following day or the next, if the first day's results are not unexpectedly favorable, the morning dose is increased by 5 or 10 units, making the total injection 15 to 20 units, or if desired one may wait for a day or two for the figures to become steady before raising the dosage. Whichever plan is followed, the glycosuria ultimately falls to 2 to 5 gm. per day or thereabouts. At this stage, without waiting for complete desugarization, one may increase the diet again by a measured number of grams G, again establish a steady excretion, and again raise the insulin dosage by an amount equal to ½ of that calculated as necessary for complete desugarization; or, one may advance the diet and the insulin coincidently to save time. We first proceeded in the first way; later, knowing better the value of the preparations, more often in the latter way. There is an advantage in the latter in that the establishment of a rather heavy glycosuria tends to retard or beat down a rising natural tolerance, thus necessitating more time and insulin to accomplish what is desired than is the case if the patient is never permitted to develop a heavy glycosuria. But the former method would seem to be safer and to give more exact information, so that for one beginning the use of insulin it is preferable. In such a case as that under discussion the patient's own tolerance may begin to rise under the effects of relief from the excess of sugar in circulation, and it may rise so rapidly that what is for the moment a necessary dose of insulin becomes an overdose. A further increase in such a situation is naturally undesirable.

As the diet is increased stepwise the time comes when a decision must be made as to the limit. This will depend upon circumstances. Injections of a volume of more than 3 cc. of any strength daily offer mechanical difficulties and the mere volume necessary may determine a practical limit. It is preferable to keep the volume within 1 or 2 cc. per day for the long run. When using 20 unit material this is a dose of 20 to 40 units. The cost is also an item. It has been our practice to consider the size of the patient and the nature of his life and work. If a diet containing the equivalent of 120 gm. glucose and 18 times that number of calories (i.e. 2100 calories in round numbers) offers a physical and economic solution of that patient's problem he is placed on such a diet if possible with the least loss of time. A larger man doing more physical work may be unable to follow his occupation on a diet with a G of only 120 and may require

140 or more if he is not to become financially dependent. This man should receive a satisfactory diet to solve his own particular problem. Again, if a man requires 140 and can burn 120 without insulin, he needs very little insulin anyway to bridge the gap between full working power and disability, but if he is able to burn only 50 gm. without insulin he will require insulin equivalent to 90 gm. to solve his problem. This would entail the daily use of perhaps 4 to 5 cc. of the product (at 20 units per cc.) and the volume itself may deter one from proceeding so far.

Cases in which by diet adjustment alone it is possible to preserve life, health and working power without disability have not been considered as insulin cases.

Temporary Uses of Insulin: Many cases present in which diet adjustment offers a solution but for which time can be saved by the temporary use of insulin. Thus, to desugarize and restore tolerance in a certain case may require 2 to 3 weeks on diets below that on which the case leaves the hospital. The undernutrition and the time and money spent on the partially disabling regimen can be avoided by the interrupted use of insulin. Desugarizing the patient by means of insulin on a higher diet permits in suitable cases a restoration of natural tolerance, like that attainable through desugarization by diet depression but with less discomfort to the patient. We have frequently given insulin to hasten desugarization or in lieu of cutting the diet below a certain level. After desugarization the insulin has then been withdrawn gradually or abruptly with no return of glycosuria.

Insulin in Pre-coma: In cases of severe acid intoxication the practice has been to institute a diet containing protein 0.5 to 0.75 gm. per kg., fat 2.0 to 2.5 gm. per kg., with the carbohydrate as low as feasible. The patient is given at once 20 gm. of the bicarbonate of soda by mouth, after which a reading is made of the volume percentage of CO_2 liberated from the plasma when examined by the Van Slyke method (i.e. the plasma bicarbonate or CO_2 combining power). Soda is then given by mouth at the rate of 15 to 20 gm. per hour until the blood plasma shows a reading of 40 to 45 vol. per cent. CO_2 by Van Slyke, or until from the symptoms and signs this procedure is deemed unnecessary. When insulin is used effectively one usually stops the soda after giving only 20 to 60 grams. In certain severe emergency cases in which it is impossible to know in advance what the glucose excretion will

be in the first 6 to 12 or 24 hours after admission, insulin has been given to check acid production without knowing how much sugar the patient will excrete in a given period of time. In such cases large doses (40 to 80 units) have been given quickly with the view to providing for the oxidation of 40 to 80 gm. of glucose in excess of any that might burn without insulin, in order to annul acid production. To insure against over-dosages of insulin under such conditions sugar has been given by stomach prior to the administration of the insulin, and thereafter in quantity sufficient to provide all of the insulin given with enough glucose to act upon without making any allowance for the glucose that might arise from the diet and endogenous sources. Thus, if a single dose of 60 units of insulin were calculated to throw into oxidation 60 to 90 gm. of glucose in 10 hours, or on the average 6.0 to 9.0 gm. per hour, then at least that quantity of sugar has been given hourly to insure against the possibility that the glycosuria was on the decline when the insulin was given and would fade out rapidly thereafter, leaving the patient with not enough glucose to counteract the insulin given. This procedure has been used only as a temporary emergency measure. It may be superfluous to mention that diabetic patients in acid poisoning who have received no insulin not infrequently before death pass urine free of sugar and acetone bodies (provided no infection complicates the case) simply as the result of the limitation of the intake of food occasioned by the general condition. To give insulin to a patient naturally approaching this juncture and without giving sugar might lead to serious insulin poisoning. With cases in which as a result of infectious complications the overproduction of acid tends to continue in spite of diet restrictions, insulin has made it possible to stop acid production and thus avoid the continued use of alkali, besides permitting of adequate nutrition. This has proved of very great value and especially in complicated cases.

Diagnostic Use of Insulin: Certain cases of the general order of those that are called renal glycosuria have been treated with insulin. A certain case shows steadily 2 to 3 gm. of glucose in the urine on a diet with a glucose value of 100 gm. On a diet with a glucose value of 200 gm. he passes on the average 4 to 6 gm. of sugar in the urine. With the dietary G equal to 400 he passes 8 to 10 gm. He has few of the ordinary symptoms of diabetes, the sugar having been discovered during an insurance examination. The blood sugar percentage ranges between 0.1 and 0.12.

Doses of 5 and 10 units of insulin have exerted little effect on the glycosuria in several such cases. This observation with variations, made on a number of cases showing no sharply definable tolerance limit, suggests the possibility of using insulin in differential diagnosis.

Determining the Value of a Given Preparation of Insulin: Individuals who have long suffered from severe diabetes and who for a period of years have not under any circumstances developed more than a certain maximum tolerance afford the most favorable medium for accurately gauging the number of grams of glucose that will be thrown into utilization by a given volume of insulin solution. Individuals whose glucose tolerance is known to be subject to fluctuation in response to factors other than insulin administration are not suitable cases to employ for the purpose of standardizing preparations. Again, early or mild cases of any kind are not dependable because if they have fixed or relatively fixed tolerance limits there is no way of demonstrating this except by the passage of time. Complete or nearly complete desugarization of the urine in any case of diabetes may be and commonly is followed by a lesser or greater increase of natural tolerance whether the desugarization be effected by diet adjustment alone or diet adjustment plus insulin. Hence if a certain diabetic individual on a fixed diet be excreting steadily 10, 20 or 30 gm. of sugar in the urine daily, and if after receiving a certain volume of insulin solution he pass urine that is sugar "free" or nearly so, it does not follow that the insulin injected has accounted directly and *per se* for all of the glucose that has disappeared from the day's urine. The desugarization or radical reduction of circulating sugar may result in a rising production of insulin from endogenous sources, and this endogenous insulin by adding its effect to that of the insulin actually injected from without may make it appear that the latter has a greater potency than it actually has. With these considerations in view it has seemed appropriate to select with great care for standardizing purposes old cases with long metabolic records, whose tolerances have long remained fixed or relatively fixed at low levels. Such cases have then been placed on regimens which permit them to excrete steadily 20 to 30 gm. of sugar per day. They have then been given doses of insulin that reduce the sugar excretion definitely but without approaching complete desugarization. If 10 units of a preparation given under such conditions lowers the

glucose excretion from an average of 25 to an average of 15 gm. per day it may be assumed that 1cc. has accounted for the utilization of 10 gm. of glucose. If the dose of insulin is then discontinued while other conditions remain as before, and the sugar excretion then rises to its former level, confirmatory evidence is added. However, should the glucose excretion remain depressed after withdrawing the insulin, this would suggest an improvement of tolerance and the test would be indecisive. Working with selected cases and in this way, we have found that 1 rabbit unit increases glucose combustion by approximately 1.0 to 1.5 gm. with considerable consistency.

Cases have been seen in which 1 unit reduced glycosuria by as much as 3.0 gm. per unit and others, especially mild arteriosclerotic cases and cases of so-called renal glycosuria, in which insulin exerted remarkably little effect.

Results: Since beginning the use of insulin one case has died of pneumonia although free of diabetic symptoms during the disease. One case with an empyema died during management suddenly before the glycosuria was eliminated and while hyperglycemia still prevailed, in cardiac collapse. One case received in extreme inanition and unable to speak because of weakness, but free of glycosuria, was given a large increase of diet and a calculated dose of insulin. On admission the blood sugar reading was not made. This case developed hypoglycemic convulsions and the blood sugar was then at a level too low to read. Sugar administrations restored a hyperglycemia and gross glycosuria, but the patient died without regaining consciousness. Subsequently a similar diabetic case received on another service died a similar death with a similar absence of blood sugar but without having received insulin. Williams of Rochester has described an analogous case of fatal hypoglycemia with convulsions due to inanition without insulin. Our own case was diagnosed as one of fatal hypoglycemia induced by an over-dosage of insulin. In retrospect, it would seem probable that the patient had been gravely hypoglycemic before the insulin was given, and had the diet been increased until glycosuria had recurred before giving the insulin the fatality probably would have been averted. The precarious state of the patient made it seem necessary at the time to hurry with extra food and the means to utilize it. The case is cited to illustrate the danger of even a moderate overdose of insulin in a profoundly undernourished case. Except for the

above mentioned case, all of the patients so far treated are living, on diets that fulfill their legitimate needs for food.

Shall the Insulin Case be Kept Sugar-free?

Old cases with low fixed tolerance limits have been found difficult to keep sugar-free at all times, owing to unavoidable variations of diet, insulin dosages, exercise, etc., and it would not seem necessary that they do so, since they seem to have no natural tolerance to lose. On the other hand, all cases that have a considerable natural tolerance or power to regain such should be kept sugar-free if possible, and it has been found to be possible in most cases.

CLINICAL OBSERVATIONS WITH INSULIN

1. The Use of Insulin in Diabetic Treatment

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INTRODUCTION.

This paper will describe our clinical experiences with insulin* from the beginning of its therapeutic trials in the United States in August, 1922, to the present time, May, 1923. This was a pioneer period of difficulties and experimentation. The results, though highly beneficial, cannot be regarded as the best that can be accomplished with insulin. Many questions concerning both aims and methods in the new treatment are still unsettled, and the divergences already apparent between different investigators will probably become deeper before anything like agreement is reached. Banting and his associates [1, 2, 3, 4, 5] have led the way in the clinical application of his discovery, and have established the general facts of the therapeutic action of insulin and the occurrence and prevention of the chief immediate danger, namely hypoglycemia. All other clinical experiences have been essentially a confirmation and extension of these basic observations.

The 161 patients in our series comprise the largest group yet treated with insulin under conditions of thorough and prolonged control, and advantage has been taken of the special opportunities offered by this Institute for experimental studies in this connection. Partly, such studies were in fulfillment of the agreement under which insulin was received. Partly, they were necessitated by the small supplies which had to be divided among a considerable number of severe cases; thus it will be noticed in the records that patients were often kept for long periods on inadequate dosage, waiting for larger supplies to complete the benefit thus begun. Also some patients, especially those living at a distance, preferred to remain in the Institute rather than risk the dangers of home treatment with the variable strength of the early lots of insulin. Others have spent a considerable time in the Institute for reasons of personal preference, and a number of charity or semi-charity cases were also available which have been under continuous observation here for several years past.

Generally it has been as convenient for all concerned to enlarge the diet with one foodstuff at a time and observe the effects for a sufficient period before making another addition. Furthermore, increased knowledge of the action of insulin has been re-

* The preparation used was the Iletin of the Eli Lilly Company, which was supplied to us under the authorization of the Insulin Committee of the University of Toronto. We take pleasure in thanking the members of this Committee and also Dr. G. H. A. Clowes of the research staff of the Eli Lilly Company for numerous favors and unfailing cooperation. They deserve the highest credit for the efficiency and rapidity with which they have developed the discovery of insulin and placed it as a reliable therapeutic agent in the hands of the medical profession. A number of imitations bearing similar names, some of them recommended to be taken by mouth, should be warned against as fraudulent.

garded as chiefly important to the diabetics themselves individually and collectively, and they have been plainly informed when they were serving experimental purposes. Patients of all classes have cooperated most willingly and loyally in these tests. The information thus gained has been used to guide the practical treatment as outlined in this paper, and it has also established some scientific facts concerning the physiological role of insulin, as described in the second and third papers of this series.* These facts are not new, for we have long regarded them as proved by our former observations with animal experiments and the diet treatment of patients, but by means of insulin they are corroborated in a manner less subject to doubts and errors. This phase of the use of insulin is new, in the sense that it has not been covered by the Toronto workers or others, and it may not only settle some old disputes but also help to guide the new investigations concerning the function of insulin in the body.

The 102 cases selected for publication are those which have been under insulin treatment for at least 2 months, or which represent acute emergencies or other instructive features. For convenience of reference in all three papers, all the case histories will be summarized here together in numerical order. This makes a jumbled arrangement from the standpoint of consecutive reading, and it may therefore be found best to defer the reading until the cases are discussed subsequently by groups.

Case No. 2. (Juvenile diabetes under accurate observation for 6 years. Improved nutrition with insulin.) This patient was No. 76 in the Rockefeller Institute series.[6, 7] He was received there as a 4 year old boy with diabetes of less than a month's standing, March 9, 1917. His record and also his picture[16] have been published as evidence of the possibility of preventing downward progress without undue sacrifice of nutrition when a juvenile case is thoroughly treated from the first mild stage. An unusual number of infections, from which the others in his family suffered as well as himself, finally reduced the tolerance slightly, and following an influenza attack in August, 1922, the parents found difficulty in adjusting the diet, and placed the boy in this Institute September 13, 1922. At the Rockefeller Institute the boy was 3 feet 6½ inches tall and weighed 33 lb. At this admission in 1922 he was 4 feet 2 inches tall and weighed 50 lb. Glycosuria ceased within two days, but it was considered desirable to begin the use of 1 unit of insulin daily in order to avoid undernutrition. The dosage was increased to 2 units on October 15, following which time a gradual increase of diet to 60 gm. protein, 50 gm. carbohydrate, and 1400 calories resulted in glycosuria on November 19 to 23. This was controlled only by the use of 9 units of insulin. Since his discharge on De-

* These two papers will appear in the Journal for January, 1923 (Vol. 3, No. 1).

cember 20, the boy has had no difficulty in remaining sugar-free on this program at home, and is entirely well and strong at his same weight of 50 lb.

Case No. 3. (Accurate observation since 1916. Loss of tolerance from stealing fat. Stationary low tolerance for past 3 years. Improvement with insulin. High dosage for gain of weight.) Admitted to Rockefeller Institute March 6, 1916, at age of 15 years. Height 5 ft. 2 in. Weight 110 lb. maximum and at admission. Family history negative except for diabetes in a paternal grandfather. Personal history negative. Apparent duration of diabetes less than 5 months. This patient was No. 66 in the Rockefeller Institute series, and has been described in several former publications [6, 7] as an example of downward progress with high calories and stationary condition with restricted calories. For the past three years her diet has been fixed at 50 gm. protein, 5 gm. carbohydrate and 1000 calories, except for temporary reductions required by violations of diet. She was admitted to the Physiatric Institute five times for such reasons from 1919 to 1922. In the summer of 1922 there were further difficulties, probably resulting from the desire to receive insulin. After minor violations of diet and repeated undernutrition at home, she was received for her sixth admission August 23, 1922, with height 5 feet 3¼ inches, weight 78 lb., and plasma sugar 0.150 per cent. One day of a diet of 60 gm. protein, 25 gm. carbohydrate and 1300 calories raised the plasma sugar to 0.175 per cent., and insulin treatment was begun with 2 units daily. By the evening of the first day the plasma sugar fell to 0.108 per cent. Thereafter it rose, so that moderate hyperglycemia of 0.14 to 0.20 per cent. was continuous during the following two months. In other words, 2 units of insulin daily provided for the assimilation of approximately 300 extra calories (including 10 gm. protein and 15 gm. carbohydrate) during this period. The weight remained at approximately 80 lb. During the following one week the diet was increased to 65 gm. protein, 30 gm. carbohydrate and 1500 calories, and the insulin to 4 units daily, on which program the patient was discharged Oct. 29, 1922, without glycosuria and with plasma sugar of 0.140 per cent. in the morning and 0.137 per cent. in the evening.

Violations of diet at home resulted in occasional glycosuria, as the patient was determined to have more food and more insulin. In a seventh admission for one week following Nov. 26, the diet was increased to 65 gm. protein, 30 gm. carbohydrate and 1600 calories, and 8 units of insulin controlled glycosuria but not hyperglycemia.

Trouble returned at home, and instead of giving more insulin, glycosuria was stopped by cutting the diet to 900 calories. When the supply of insulin became larger, the patient was brought back for her eighth admission Jan. 8, 1923. Diet and insulin were increased week by week in such manner that glycosuria was constantly absent but hyperglycemia of approximately 0.2 per cent. constantly present. On this basis a diet of 80 gm. protein, 50 gm. carbohydrate and 2000 calories required approximately 20 units of insulin for assimilation at a weight of 90 lb. A diet of 80 gm. protein, 60 gm. carbohydrate and 2500 calories required ap-

proximately 24 units of insulin at a weight of 94 lb. The patient was discharged Feb. 24, 1923, on a diet of 100 gm. protein, 150 gm. carbohydrate and 3000 calories. Glycosuria was present at discharge and has returned repeatedly at home as the body weight has risen. Its control has required successive increases of insulin, until recently at a weight of 123 lb. the patient has required 60 units of insulin daily, divided into four injections. As obesity is undesirable, the diet has been reduced to 2500 calories by reducing the fat without changing protein or carbohydrate. Exercise is to be increased, and it should be possible to reduce the insulin dosage. The patient follows the diet because it is pleasant and satisfying. She is now continuously free from glycosuria, and looks and feels entirely well.

Case No. 24. (Severe diabetes with nephritis, under continuous observation in Institute for over 3½ years. Insulin requirement for fat and carbohydrate. Greatly improved nutrition. Photographs: Figures 1 and 2 before insulin, Figures 3 and 4 after insulin.) Male. American. Age 27 years. Height 5 feet 6 inches. Weight 140 lb. maximum, 92 lb. at admission, August 4, 1919. Diabetes had been present for six years, and though treatment had been followed most of the time, downward progress has been very marked. Since his admission, Aug. 4, 1919, he has lived continuously in the Institute. Here a serious complication developed in the form of renal calculi and infection, which left behind a permanent nephritis. With undernutrition, the diet was built up to 50 gm. protein, 10 gm. carbohydrate and 1000 calories, and a constant weight of 80 lb. was maintained. The patient thus remained free from perceptible downward progress for three years. He was occupied with light clerical work all day long, and was comfortable except for the degree of emaciation and weakness. His history up to this point has been previously published.[8,9] At the beginning of September, 1922, he experienced sudden malaise and indefinite pains suggestive of his former experience with urinary gravel. Nothing definite was found clinically or in the urine, but the plasma sugar rose sharply and glycosuria was prevented only by a sudden reduction of diet to 500 calories. The disturbance gradually passed off and the diet had been built up to 850 calories with normal plasma sugar by November 4, when insulin treatment was begun.

Details of the later record are given in paper 3 (Table 14). The diet was gradually built up to 60 gm. protein, 75 to 150 gm. carbohydrate and 2213 calories, which is fully assimilated with the aid of approximately 40 units of insulin per day. The weight has risen to 90 lb. and the strength is decidedly improved. The process of upbuilding is still in progress.

Case No. 54. (Severe diabetes, under continuous observation in Institute for 3½ years. Insulin requirement for protein, carbohydrate and fat. Greatly improved nutrition.) Female. American. Age 40 years. Height 5 feet 4 inches. Weight 150 lb. maximum, 120 lb. at admission, Sept. 28, 1919. The condition prior to insulin treatment has been described in previous papers.[8,9]

Rigorous undernutrition succeeded at first in establishing a tolerance for 1050 calories, but after a few slips in diet at home the utmost tolerance was only 45 gm. protein, 3 gm. carbohydrate and 800 calories, at a weight of 62 lb. The severe measures employed kept the patient alive three years after admission, and she could probably have lived a year or two longer, but final death from inanition was made inevitable by the inability to acquire tolerance for a living diet. Changes of weight and strength were so slow as to be almost imperceptible, but instead of being up all day, the patient gradually became too weak to be up more than half a day and was capable of only the smallest exertion.

Insulin treatment was begun August 10, 1922, but up to Feb. 1, 1923, the dosage did not exceed 4 units per day. Since then, the dosage and diet have gradually been raised, as shown in paper 3 (Table 16). The weight has increased to 85 lb., and the strength is very materially improved, although the result is still very incomplete.

Case No. 70. (Moderate diabetes becoming severe with abandonment of diet. Approximate estimate of downward progress in terms of insulin. Insulin requirement for carbohydrate and protein. Clinical improvement.) Male. Norwegian-American. Age 28 years. Height 5 feet 9 inches. Weight 160 lb. maximum, 125 lb. at admission, Oct. 6, 1919. Family history negative. Personal history—usual childhood infections; typhoid with three relapses in 1912; occasional indefinite abdominal pains since. Three weeks before admission, the patient had acute rhinitis with headache, followed in two days by excessive hunger and thirst and polyuria. Diabetes was then diagnosed, but as the weight at this time was only 136 lb., the real onset may have been earlier. Treatment was entirely ignored until serious loss of weight and strength and threatening acidosis symptoms caused him to come to the Institute.

Heavy glycosuria and slight ketonuria were present, the plasma sugar was 0.357 per cent., and coma symptoms were absent. On a diet of 50 gm. protein and 10 gm. carbohydrate, glycosuria ceased within three days and the plasma sugar was normal on the sixth day. The patient was discharged Sept. 11, 1919, on 70 gm. protein, 25 gm. carbohydrate and 2000 calories, at a weight of 114 lb. Undernutrition to the extent of a reduction of 11 lb. in weight since admission had been imposed chiefly with a view to creating a tolerance for this high diet, inasmuch as the patient had to support his family as a carpenter and was stronger with this diet at a lower weight than with a lower diet at a higher weight.

As his strength was not fully normal, the patient was tempted to add slightly to his diet, and for some months was free from glycosuria. Repeated returns of glycosuria then caused him to discard all treatment and downward progress was soon evident. He was readmitted Oct. 31, 1922, weighing 110 lb., with heavy glycosuria and ketonuria, plasma sugar of 0.555 per cent., and plasma bicarbonate of 35.7 vol. per cent. After a diet of 15 gm. protein and 25 gm. carbohydrate for five days had cleared up the acidosis, a diet of 30 gm. protein and 5 gm. carbohydrate with no more than 16 gm. fat daily was continued to Nov. 27. On Nov. 8, as the patient was still excreting 26.6 gm. of sugar with a D:N ratio of 2.75,

insulin treatment was begun. The severity of the case at this stage is indicated by the fact that on the low diet mentioned, an increase of insulin to 6 units was necessary to stop glycosuria on Nov. 20, and dosage of 12 units had not reduced the plasma sugar below 0.153 per cent. on Nov. 27.

Further details are given in paper No. 2 (Table 7). It will be noticed that from Dec. 24 to Jan. 31 the diet was 90 gm. protein, 25 gm. carbohydrate and 1700 calories, i.e., slightly lower than the 70 gm. protein, 25 gm. carbohydrate and 2000 calories on which the patient was first discharged. The dosage of insulin required for the 1700 calory diet was found to be 24 units per day. The apparent rise in body weight was due chiefly to edema, and the true weight at this time was probably not greater than at the first discharge. From this comparison, it seems evident that the patient had lost tolerance to the extent of at least 24 insulin units per day, as the result of his violations of diet. Such figures stand in strong contrast to the stationary tolerance or slight downward progress of patients who have tried to be faithful to treatment.

The patient was discharged March 30, 1923, on a diet of 90 gm. protein, 140 gm. carbohydrate and 3500 calories, with 40 units of insulin divided into three doses per day. His weight has risen to 142 lb. and his strength has improved so that he has become able to return to carpenter work.

Case No. 85. (Severe diabetes, under continuous observation in Institute for 3 years. Insulin requirement for carbohydrate and fat. Improving nutrition.) This patient has been described in former publications.[8,9] In brief, he is a physician who developed diabetes as a medical student in May, 1915, at the age of 26 years, and during the following four years progressed downward steadily and markedly on accurately regulated diets which aimed to keep glycosuria absent but ignored hyperglycemia. With a height of 5 feet 10 inches, his maximum weight had been 178 lb. and his average weight 155 to 165 lb., and on admission to the Institute in November, 1919, his weight had fallen to 111 lb. The blood sugar was made normal by undernutrition which reduced the body weight to approximately 100 lb., and a diet of 50 gm. protein, 5 gm. carbohydrate and 1100 calories was gradually built up. Numerous trials showed that this diet could not be exceeded without hyperglycemia or glycosuria. In the three years up to 1922, there was absolutely no loss of tolerance; on the contrary, a slight improvement permitted increasing the diet to 55 gm. protein, 10 gm. carbohydrate and 1200 calories. The average of these rations was slightly reduced by the usual day of partial fasting each week. Constant weight and nitrogen equilibrium were maintained. The patient was a comfortable and contented invalid, who was capable of moderate walks and light amusement but was unfit for either physical or mental work and doubtless could not live outside of a special institution.

Insulin treatment was begun November 4, 1922, after almost precisely three years of continuous residence in the Institute, in the attempt to build up weight and strength and restore usefulness if possible. Details of the record are given in paper 3 (Table 17). Beginning with 1 unit per day, the insulin has gradually been increased to 33 units per day, which

at least temporarily provides for the assimilation of an experimental diet of 60 gm. protein, 90 gm. carbohydrate and 3860 calories. The weight has risen only to 118 lb., and the increase of strength, though distinct, is less than in any other of the patients treated. This imperfect result is to be attributed only to the incompleteness of the treatment to date.

Case No. 172. (Moderate diabetes. Improved condition and fidelity with insulin.) Hebrew. Age 32 years. Had diabetes of one year's known duration at the time of his first admission to the Institute, February 29, 1920. His mother has had diabetes for 15 years, and one of his two sons developed diabetes at the age of 4 years. This child was treated with diet for several months, and then was allowed to die through carelessness of the parents, apparently because they did not consider it worth while to keep him alive by extreme care in a semi-invalid condition. The patient seemed to display a similar attitude toward his own diabetes. At the time of his discharge, March 11, 1920, he had normal blood sugar on a diet of 50 gm. protein, 20 gm. carbohydrate and 1400 calories, and could doubtless within a few weeks have increased this diet appreciably. He was dissatisfied with his reduced strength under diet treatment, and almost immediately broke off treatment and allowed sugar to return. On account of insulin, he came for re-admission October 18, 1922. He had progressed downward so that his uncontrolled diet could no longer keep him strong enough for work. With a height of 5 feet 8 inches, he had lost in weight from his former 130 lb. to 115 lb. He became sugar-free on three days of 25 gm. protein and 5 gm. carbohydrate, but was unable to tolerate his former diet. Insulin was begun without waiting to ascertain his exact tolerance and was gradually increased to 18 units per day. With this, he has become able to tolerate a diet of 90 gm. protein, 65 gm. carbohydrate and 2500 calories. He follows the treatment faithfully and reports regularly for tests.

In this case also, the breaking of diet resulted only from a definite determination to eat in order to be as strong as possible for as long a time as possible. With insulin, the patient feels well and strong and is convinced that the treatment is worth the trouble. He therefore is faithful to the combined use of diet and subcutaneous injections, though he would not adhere to the treatment by diet alone.

Case No. 174. (Very severe diabetes. Extreme undernutrition for 2½ years. Insulin requirement for carbohydrate and protein. Clinical improvement.) Female. Jewish-American. Age 42 years. Height 5 feet 2 inches. Weight 115 lb. maximum, 86 lb. at admission, March 7, 1920. Family and personal history unimportant. Thirst, polyuria and loss of weight were noticed in October, 1918, and diabetes was diagnosed two months later. A diet restricted only in carbohydrate failed to stop glycosuria, and weight and strength were lost steadily. At admission, the patient was weak and tired, with heavy glycosuria, comparatively slight ketonuria, plasma sugar of 0.437 per cent., marked plasma acetone reaction, and plasma bicarbonate of 43.3 vol. per cent. After three days of a diet of only 30 gm. protein, complete fasting for one week cleared the urine, but the plasma sugar was still 0.250 per cent. The trivial

tolerance then necessitated prolonged undernutrition in order to build up any diet. The patient was finally discharged Oct. 2, 1920, weighing 75 lb., on a diet of 50 gm. protein, 5 gm. carbohydrate and 800 calories, with plasma sugars ranging between 0.128 and 0.156 per cent. On account of her age, it was hoped that this slight hyperglycemia might be borne without harm, but any higher diets had been found to give rise to glycosuria.

Though the patient was an extremely poor and uneducated tenement dweller, she followed treatment with religious scrupulousness. The low diet, especially when reduced by the weekly days of partial fasting, was not quite adequate for maintenance even with her small size and minimal metabolism. Furthermore, the slight hyperglycemia evidently represented overtaxed function and tended very slowly to increase, requiring occasional short periods of semi-starvation to prevent glycosuria. She was admitted to the Institute on two further occasions when the home treatment was ineffectual. When admitted for the fourth time, Nov. 20, 1922, for insulin treatment, she weighed 67 lb. and had hyperglycemia of 0.220 per cent. without glycosuria. Two points may be noticed in regard to this excessively rigorous undernutrition. First, on an abundant diet limited only in carbohydrate the patient had lost 29 lb. in one and a half years, while with the extreme undernutrition she lost only 19 lb. in two and a half years. Second, though she lived the life of an emaciated invalid and death from inanition seemed to be the ultimate prospect, this treatment was the only possible means whereby a patient with diabetes of this severity could have been kept alive to receive salvation through insulin. The detailed record is given in paper No. 2 (Table 21). The patient is still in the Institute, and up to the present her diet has been raised to 1650 calories—i.e., approximately doubled—with the aid of 20 units of insulin divided in two injections per day. The strength has increased out of proportion to the weight, and the general appearance is also disproportionately improved. With a more rapid increase of diet, it is hoped that the patient before long will be able to resume the earning of wages which are seriously needed by her family.

Case No. 191. (Severe diabetes, controlled by low diet since 1914. Marked improvement with insulin. Insulin requirement for increased diet. Death from unknown complication.) Male. American. Height 5 feet 9¼ inches. This patient was No. 24 in the Rockefeller Institute series,[6, 7] and was carried into the Rockefeller Institute Hospital Nov. 28, 1914, in a supposedly dying condition. He was then 44 years of age and the diabetes was of 8 years' duration. He had the usual severe symptoms, and had emaciated from his ordinary weight of 165 lb. down to 97 lb. His weight at the end of treatment was practically identical, though there was doubtless some loss of tissue and retention of water with the rigorous undernutrition required for control of the condition. His tolerance was built up to 50 or 60 gm. protein, 10 gm. carbohydrate and 1500 calories, which barely sufficed to keep him stationary at his low body weight. In this emaciated condition he carried on active supervision of his factory through the intervening years, without disability and without

TABLE 1

Case No. 191

Date 1923	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Jan.								
25	80	124	40	1600	15.54	336	...	2
26	"	"	"	"	7.86	...	106	2
27	"	"	"	"	.....	341	...	2
28	"	"	"	"	.....	...	106	6
29	"	"	"	"	10.44	...	...	6
30	"	"	"	"	9.24	349	105	6
31	"	"	"	"	3.00	...	103	10
Feb.								
1	"	"	"	"	+	...	...	10
2	"	"	"	"	0	...	102	10
3	"	"	"	"	0	211	101	10
4	"	"	"	"	0	...	98	10
5	"	"	"	"	0	...	...	10
6	"	"	"	"	0	...	97	10
7	"	"	"	"	0	168	96	10
8	80	97	100	1600	0	...	...	10
9	"	"	"	"	0	...	95	10
10	"	"	"	"	0	...	...	10
11	80	120	160	1800	0	...	...	10
12	"	"	"	"	0	214	91	10
13-17	"	"	"	"	0	...	91	10
18	"	"	"	"	0	209	90	10
19-20	"	"	"	"	0	...	89	10
21	"	"	"	"	1.92	...	...	12
22	"	"	"	"	1.71	...	...	12
23	"	"	"	"	+	...	88	12
24	"	"	"	"	+	...	...	12
25	90	137	100	2000	2.53	263	89	12
26	"	"	"	"	2.19	...	...	12
27	"	"	"	"	0	...	92	12
28	100	133	100	2000	+	...	92	14
Mar.								
1	"	"	"	"	13.82	349	92	14
2	"	"	"	"	10.56	...	...	14
3	"	"	"	"	9.87	...	...	14
4	"	"	"	"	7.59	...	92	18
5	"	"	"	"	14.54	323	93	18
6	"	"	"	"	11.63	...	93	18
7	"	"	"	"	6.63	...	...	18
8	"	"	"	"	++	...	93	24
9	"	"	"	"	++	...	...	24
10	"	"	"	"	4.28	...	93	24
11	"	"	"	"	0	...	...	24
12	"	"	"	"	0	...	...	24
13	"	"	"	"	0	...	95	24
14	"	"	"	"	0	200	...	24
15	"	"	"	"	0	...	93	24
16	"	"	"	"	0	...	...	24
17	"	"	"	"	0	...	94	24
18	"	"	"	"	0	...	...	24
19	100	189	100	2500	0	...	95	24
20	"	"	"	"	0	...	...	24

TABLE 1.—*Continued*

Date 1923	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Mar.								
21	100	189	100	2500	0	270	96	24
22	"	"	"	"	0	...	...	24
23	"	"	"	"	0	...	96	24
24	"	"	"	"	0	...	...	24
25	"	"	"	"	0	...	97	27
26	"	"	"	"	0	283	98	27
27	"	"	"	"	0	...	...	27
28	"	"	"	"	0	238	100	30
29	"	"	"	"	0	...	100	30
30	"	"	"	"	0	...	...	30
31	"	"	"	"		326	99	30
April								
1	"	"	"	"	0	...	...	36
2	"	"	"	"	0	...	100	36
3	"	"	"	"	0	118‡	...	36
4	"	"	"	"	0	250	99	36
5	"	"	"	"	0	217	...	36
6	"	"	"	"	0	110‡	101	36
7	100	189	116	2564	0	69‡	...	36
8	100	189	100	2500	0	242 98‡	100	36*
9	"	"	"	"	0	246	...	36*
10	"	"	"	"	0	263 120‡	102	36*
11	"	"	"	"	0	306 162‡	102	36*
12	"	"	"	"	0	226 110‡	...	36
13	"	"	"	"	0	242 97‡	103	36
14	"	"	"	"	0	200 234‡	...	36
15	"	"	"	"	0	300 97‡	103	36
16	"	"	"	"	0	250 166‡	...	36
17	"	"	"	"	0	230 90‡	103	36
18	"	"	"	"	0	192	104	36
19	"	"	"	"	0	90†	103	36*
20	"	"	"	"	+	...	...	36*
21	100	189	132	2628	1.80	...	104	32*
22	100	189	100	2500	0	...	...	32

*Rest days.
‡Blood samples taken at 7 p.m.
†Blood sample taken at 10 p.m.

decline of tolerance. In December, 1922, an attack of influenza forced him to reduce his diet to 700 calories in order to avoid glycosuria. He developed marked ascites and slight edema of the ankles, which did not clear up when he went to Florida for convalescence. He accordingly came to this Institute Jan. 15, 1923.

At this admission, his plasma sugar was at the normal level of 0.114 per cent. The apparently increased weight of 106 lb. was due to hydrops, as the patient had lost several pounds with his recent illness and was distinctly weaker than before. His assimilative function was evidently returning, as a preliminary diet of 60 gm. protein, 25 gm. carbohydrate and 1200 calories seemed to be tolerated. An increase to 80 gm. protein, 40 gm. carbohydrate and 1600 calories caused glycosuria, as shown in the detailed record in Table 1.

The ascites was not accompanied by signs of any organic disease, and finally appeared to be only a peculiar localization of the well-known malnutrition edema, as it began to diminish with salt-free diet before the use of insulin, and subsequently disappeared quickly in the course of the insulin treatment. The patient attained to a diet of 100 gm. protein, 100 gm. carbohydrate and 2500 calories, for which approximately 30 units of insulin per day was needed. His strength and appearence improved greatly, but after the prolonged emaciation the gain in weight was slow, supposedly because water has been driven out as fat and other materials have been deposited. He remained free from edema or ascites without any serious restriction of his salt intake, and looked forward to returning home soon in a nearly normal condition.

Though this patient arrived in practically a bed-fast condition, since the early part of March he took exercise to the extent of walking approximately 3 or 4 miles daily. With the dosage of 36 units of insulin, which began April 2, hyperglycemia was always well marked in the blood samples taken before breakfast, but the evening figures were lower as usual, and by April 3 slight hypoglycemic symptoms (perspiration, weakness and nervousness) were becoming manifest. As the evening blood samples were taken arbitrarily at 7 P. M., while the symptoms began a few hours later and reached their maximum about midnight, it is evident that the lowest levels of plasma sugar are not represented in the analyses. Beginning April 4, the patient was requested to increase his walking to the limit of his strength for experimental purposes. He therefore lengthened his walks progressively on April 5 and 6, and on April 7 covered perhaps ten miles and was exhausted by the effort. The evening symptoms of hypoglycemia increased in proportion to the exercise. On April 7 the 7 P. M. analysis was noticeably low, and toward midnight a serious attack occurred which necessitated the giving of 50 cc. of orange juice and 10 gm. of pure glucose. The plasma sugar of the following morning, which was 0.242 per cent., would presumably have been lower except for this midnight carbohydrate. Complete rest was then imposed, April 8-11, on which days the patient merely sat in a chair in his room. Hypoglycemic symptoms were trivial on the evening of April 8 and absent thereafter. The rise of plasma sugar to 0.306 per cent. on

the morning of April 11 and 0.162 per cent. that evening seems significant, but no reason is known for the fall to 0.226 per cent. on the following morning. Light exercise was begun on April 12 and gradually increased on the following days. The patient was too apprehensive of hypoglycemia to undertake walking to the extent of more than a mile or two daily. Because of supposed slight symptoms on the evenings of April 17 and 18 (which the patient admitted might be imaginary, and which were complained of at 10 P. M. when the plasma sugar was no lower than 0.09 per cent.), he omitted exercise on the ensuing days. A trace of glycosuria appeared in the morning urine sample of April 20. That evening, the patient was apprehensive, and asked to have orange juice and glucose by his bed to use if necessary. By morning he had taken 32 gm. of carbohydrate, probably unnecessarily, and showed glycosuria of 1.8 gm., which may also have been due partly to a decrease of insulin dosage to 32 units. With continuance of his regular treatment and moderate exercise on the following days he remained free from glycosuria but with hyperglycemia as usual, and hypoglycemic symptoms were absent. On the whole, the experiment seems to show a distinct effect of exercise in lowering the blood sugar, but the influence is comparatively feeble, as has been recognized in connection with the diet treatment.[10, 11]

The condition and prognosis continued excellent until April 27. On this day the patient developed an annoying cough, and with much effort expectorated thick white fibrinous material. His temperature was 100° F. in the morning, 100.2 in the evening. He felt weak and had poor appetite, but was unable to account for his condition as he said his feelings were totally different from those of a cold. The urine was normal, and the plasma sugar 0.349 per cent. On April 28 the entire condition was more pronounced; there was more cough and expectoration of the tough fibrinous material; the patient remained in bed on account of weakness, and he refused food completely. The temperature in the morning was 99.4° F., but thereafter it was constantly normal, between 98 and 99. The leukocyte count was 9,400. Insulin was omitted altogether, partly because of the danger of hypoglycemia with fasting, and partly on the chance that the peculiar condition might be some form of reaction to any component of the extract. The urine remained free from sugar and acetone. The patient was cheerful and entirely clear mentally, and puzzled by his own indisposition. The physical examination from the beginning had been negative, except for indications of a slight bronchitis in the larger tubes, and though the condition was studied because of its uncertain character, it was regarded as transitory and harmless. There was no vomiting, but the patient positively refused both food and fluids, and passed no urine after noon of April 28. About midnight he developed the first alarming weakness and the rapid breathing of acidosis. A blood sample then showed plasma sugar of 0.668 per cent., plasma bicarbonate of 14.7 vol. per cent., and a moderate nitroprusside reaction in the plasma. Intensive treatment for acidosis was immediately begun, with insulin in 30 unit doses, orange juice and glucose by mouth, and also one dose of 5 gm. sodium bicarbonate. When the patient was persuaded to take these

things, it was found that they were retained without real nausea. Frequently repeated blood tests showed that the plasma sugar was falling and the bicarbonate gradually rising. The nitroprusside test of the plasma became negative. Weakness nevertheless increased; the patient's lips became blue, and his veins, though easily visible, were so poorly filled and collapsed so easily that the taking of blood samples was difficult. His skin was always yellowish, therefore jaundice was not noticed till the last day, when it increased to a fairly deep yellow color. Two more doses of 5 gm. sodium bicarbonate were given on April 29. They sufficed to relieve any serious dyspnea, and the patient remained clearly conscious and comfortable except for the increasing weakness. Death occurred at 2:30 P. M., preceded by only a few minutes of unconsciousness. The blood at this time showed the following: sugar, 0.349 per cent.; plasma bicarbonate, 31.9 vol. per cent.; nitroprusside reaction of plasma negative; urea 50 mg. per 100 cc. (as against 26 mg. that morning); plasma chloride 503 mg. per 100 cc. Catheterization after death yielded 300 cc. of clear, concentrated-appearing urine, which showed heavy sugar, slight nitroprusside and negative ferric chloride reactions, no bile, a trace of albumin, and large numbers of hyalin and granular casts. During April 29 the patient had received 170 units of insulin subcutaneously and 500 cc. of orange juice and 50 gm. of glucose by mouth. Tincture of digitalis in dosage of 2 cc. t. i. d. beginning April 28 was the only medication and was seemingly without effect.

While the terminal condition was an atypical acidosis, the cause underlying it and the other symptoms was evidently some acute intercurrent accident, but the nature of this was not diagnosed clinically and an autopsy was not obtained.

Case No. 200. (Unusually good healing of gangrene with diet and insulin treatment.) Male. Hebrew. Age 53 years. Height 5 ft. 3 in. Weight 155 lb. maximum, 145 lb. average, 130 lb. at first admission March 27, 1920, 118 lb. at readmission Dec. 27, 1922. Father died at 96, mother at 90 of old age. No history of diabetes in the family. Patient always had fairly good health. Between the ages of 18 and 45 he worked long hours and intensely. His diet has been ordinary except for overeating on special occasions. He has used large quantities of salt, but no alcohol. At the age of 18 he contracted malaria, and took large quantities of quinine for a period of five years. At the age of 26 he had a peculiar condition which was not diagnosed, but he remembers his physician telling him that his spleen was very large. He was then in bed for about six weeks, the main complaints being weakness and loss of weight, with very slight pain in the epigastrium and over the region of the spleen. At the age of 42 he had hemolytic jaundice; his skin was yellow for three or four weeks and itched severely. For six weeks he has had pain over the heart with precordial distress, and radiating pains down the arms when he overexerted. Very often the pain has been so severe that he has had to stop for a few minutes until it subsided. He has had no attacks of unconsciousness or evidences of paralysis, although the arms and legs have tingled and felt numb occasionally.

Seven years ago he was rejected for life insurance because of glycosuria. He paid no attention to diet, and considered the condition harmless until two years ago when he began to lose weight and suffered from thirst and polyuria. His physician told him to restrict starches and sugar, which he did, and the symptoms subsided. During the ensuing year his weight dropped from 150 lb. to 140 lb. He objected strongly to the limitation in diet, and practically abandoned treatment until his first admission to the Institute, April 24, 1920. He was treated in the Institute for a period of three weeks. On admission, there were heavy glycosuria, faint acetonuria, and plasma sugar of 356 mg. per 100 cc. He was in fairly good condition, although somewhat weak and undernourished. He walked slowly and carefully, for he was afraid of a return of anginal attacks, although he had not had one for four or five weeks. He was discharged on a diet of 60 gm. protein, 15 gm. carbohydrate and 1200 calories, without glycosuria and with normal blood sugar.

He was not seen again until his readmission on Dec. 27, 1922. During the intervening time he had followed diet poorly and irregularly. Sugar was present in the urine the greater part of the time, but usually only mere traces, and he checked it by fasting. His weight was 118 lb. Two months before the second admission the great toe of the right foot became painful and numb, and a small black spot about 1½ cm. in diameter appeared on the lateral surface. It gradually extended to the toe-nail, and a small amount of purulent material exuded from the matrix. A surgeon removed the nail and found the distal phalanx necrotic. X-ray examination showed osteomyelitis of the two distal phalanges. The wound refused to heal and the patient was unable to wear a shoe. He was kept awake by severe pain at night. The foot was cold and numb, but he was unable to tolerate external applications of heat, as the pain was intensified. Sugar was present in the urine almost constantly, but by rigid fasting and low diet he kept it down to fractions of one per cent.

At this admission the physical findings were as follows. The patient is an undernourished elderly male. The skin is wrinkled and dry, and has a peculiar yellowish pasty tinge. The sclerae are dull white in appearance. Conjunctivae clear. Slight arcus senilis. Eyes react normally to light and accommodation. Nose, ears and throat are normal. He wears plates in both upper and lower jaws. Lungs normal. Heart is not enlarged. He complains of oppression over the heart and intermittent palpitation. Systolic murmur over the aortic region; no murmur at the apex. Blood pressure 120/70. Radial and brachial arteries are palpable and sclerotic. The nail of the great toe on the right foot has been removed, as has the matrix, leaving a crater-like ulcer with sinus about 2 cm. deep, which exposes the periosteum of the phalanx. There is a considerable discharge of thick yellow pus. There is also a moderate cellulitis over the base of the great toe. The dorsalis pedis artery cannot be felt. The whole foot is cold and numb and slightly cyanotic. The dorsalis pedis artery on the right foot is barely palpable.

The urine was sugar-free, and the plasma sugar was 197 mg. per 100 cc. The patient at first desired to carry out treatment without the use of

insulin. By reduction of the body weight to 113 lb. within 2 weeks he tolerated a diet of 50 gm. protein, 20 gm. carbohydrate and 1200 calories without glycosuria or hyperglycemia. He was discharged to his home under the care of a trained dietitian on Jan. 9, 1923.

From Jan. 9 to Feb. 8, 1923, he continued free from glycosuria on the diet mentioned but had hyperglycemia of 0.211 to 0.246 per cent. The weight remained stationary at 121 lb. On Feb. 1 a small sequestrum was removed from the sinus. For a few days there was an increase of bloody and purulent exudate, but thereafter the toe healed much more rapidly and the superficial tissue healed and contracted quickly, although the sinus failed to close.

On Feb. 8, insulin treatment was begun with 5 units twice a day, and the diet was increased to 60 gm. protein, 40 gm. carbohydrate and 1700 calories. The dosage was increased to 15 units per day on Feb. 14 and further to 22 units on Feb. 18. By this time all evidence of cellulitis and lymphangitis had disappeared. Each day the exudate was less, and the surrounding skin was thoroughly dry and practically normal. On Feb. 18 glycosuria returned when a higher diet of 80 gm. protein, 50 gm. carbohydrate and 2000 calories was tried. This diet was given for only one week and then reduced to 80 gm. protein, 50 gm. carbohydrate and 1700 calories. After this reduction, glycosuria persisted for ten days and then disappeared. By March 19 the toe had healed entirely, was painless and showed no evidence of inflammatory reaction or gangrenous tendencies.

This result, in regard to both wound healing and general nutrition, is better than ordinarily obtained by diet treatment.

Case No. 215. (Moderate diabetes. Improved condition and fidelity with insulin. This patient was a Jewish chauffeur, aged 22 years at his first admission to this Institute, April 6, 1920. The family and personal history were negative. Diabetes was discovered in a routine examination for life insurance in 1916, when the patient was feeling entirely well. He was placed on various diets but was sugar-free only for very brief periods. His general condition was good enough that he was able to continue work, and he came for treatment only on becoming frightened at learning that he had 4 per cent. glycosuria and also on developing edema. He remained in the Institute until November 9, 1920, doing light work in return for his treatment. He was able to maintain normal blood sugar on a diet of 70 gm. protein, 20 gm. carbohydrate and 1400 calories. With a height of 5 feet 4 inches, he thus maintained a constant weight of 105 lb., and the result was clinically satisfactory under the conditions.

The patient was frightened of his diabetes, but at the same time was discontented at not being strong enough to earn a living at regular work without hindrance. He therefore ceased to report after his discharge, and was traced indirectly in various places, searching for a cure of diabetes and having glycosuria much of the time. On account of the news concerning insulin, he reappeared for readmission to the Institute on November 23, 1922. The weight was 113 lb., partly edema, and heavy glycosuria and moderate ketonuria were present. The limit of tolerance seemed to have fallen to approximately 45 gm. protein, 10 gm. carbohy-

drate and 800 calories. By means of insulin dosage, gradually increased to 15 units per day, it was possible to raise the diet to 70 gm. protein, 25 gm. carbohydrate and 2500 calories, while keeping glycosuria absent and the blood sugar nearly normal. The patient is satisfied with the treatment, because he has enough to eat and can earn his living by regular work as a chauffeur without being dependent on charity. He realizes the dangers of inaccuracy in diet or dosage, and is willing to maintain fidelity in return for the benefit received. Insulin has cured his tendency to violate diet, because the violations were due not to lack of intelligence or will but to a desire for greater strength than was possible under the conditions of strict diet alone.

Case No. 274. (Mild juvenile diabetes. Improved nutrition with moderate dosage of insulin.) Male. Jewish-American. Age 13 years. Height 5 feet 1 inch. Weight 120 lb. maximum, 98 lb. at admission, June 24, 1920. Family history negative. Measles, pneumonia, bronchitis in early years; influenza October, 1919, but urine sugar-free in January, 1920. Diabetes was diagnosed with onset of acute thirst one month before admission, but weight had been lost in preceding months.

The case was of mild early type, with only moderate acetonuria, and a tolerance for 60 gm. protein, 35 gm. carbohydrate and 1600 calories was quickly built up, at a weight of 96 lb. With strict fidelity to diet, the boy has since remained free from hyperglycemia. The ability to increase the diet to 65 gm. protein, 35 gm. carbohydrate and 1800 calories proved to be only temporary, and there was no lasting gain beyond the original tolerance. He always looked well, with rosy cheeks and bright eyes, and attended school without interruption.

He was again in the Institute, Dec. 20, 1922 to Jan. 3, 1923, and with 3 units of insulin daily became able to take the higher diet mentioned without hyperglycemia. At this admission, his height was 5 feet 1⅝ inches and his weight 95 lb., indicating inability to gain weight. At home the diet has been increased to 75 gm. protein, 40 gm. carbohydrate and 2000 calories. The insulin dosage has been increased to 6 units, divided in two injections daily, and probably must be somewhat further increased. The weight has risen to 104 lb. The boy is not only better physically and better fitted to grow, but also is much less worried over his diabetes than formerly.

Case No. 314. (Long-standing moderate diabetes. Improvement of nutrition with insulin.) Male. American. Age 56 years. Height 5 feet 10 inches. Weight 206 lb. maximum, 136 lb. at admission, August 10, 1920. Family history—diabetes in mother, nephritis and arteriosclerosis in father. Personal history—one attack of jaundice in childhood; mild typhoid fever in 1902; chronic tonsillitis and pyorrhea. Diabetes was diagnosed in 1904, but he had been troubled with crops of boils in 1903. Careful treatment has been followed from the first but nevertheless glycosuria has been present most of the time. At admission, the patient was noticeably thin and weak, free from glycosuria, but with plasma sugar of 0.233 per cent. His difficulty was that all attempts at dieting resulted in glycosuria. On a diet of 30 gm. protein, his plasma sugar

came to normal by August 19. Fat was then added to make 400 calories daily, and the diet gradually built up to 50 gm. protein, 20 gm. carbohydrate and 1200 calories, on which the patient was discharged with normal plasma sugar at a weight of 120 lb. He stopped weighing his diet and estimated it rather liberally, so that he remained constantly free from glycosuria at home but had continuous marked hyperglycemia. Thanks to his age and type of case, this did not entail downward progress, and he carried on his regular work efficiently until readmitted to the Institute Jan. 30, 1923, still free from glycosuria at an increased weight of 131 lb. He was discharged Feb. 24, 1923, on 90 gm. protein, 100 gm. carbohydrate and 2500 calories, with 20 units of insulin divided in two injections per day. Glycosuria of 9 to 22 gm. was still present, but after a gradual increase to 30 units per day at home he has remained consistently sugar-free. The weight has risen to 146 lb., and the restoration of subjective health and strength is complete.

Case No. 328. (Moderate diabetes, becoming severe with abandonment of diet. Insulin requirement for protein, carbohydrate and fat. Tuberculosis. Improved physical and psychic condition.) Male. American. Age 26 years. Height 5 feet 6 inches. Weight 155 lb. maximum, 111 lb. at admission, August 28, 1920. No diabetes or other hereditary ailments were known in the family. The patient had led an ordinary active life in the south. He entered the army on the outbreak of the war and developed acute symptoms of diabetes in February, 1918.

He had emaciated from his usual weight of 152 lb. to 140 lb. when the diagnosis was made in March, 1918. He was admitted to one of the Army hospitals immediately. Six per cent. sugar and heavy acetonuria were present, but both cleared within three days by partial fasting. The diet was gradually increased and he remained free of glycosuria until July, 1918. His weight in July was 135 lb.

He was kept in various Army hospitals from July, 1918, until August, 1919. Sugar was kept absent from the urine most of this time up to November, 1918, but he was weak, and the body weight gradually fell to 125 lb. From November, 1918, to March, 1919, glycosuria was uncontrollable and he relaxed treatment and took a general diet with the exception of bread and sugar. In March, 1919, by strenuous efforts his urine was made sugar-free by means of low diet and numerous fast days. The body weight steadily declined to 120 lb., and he became totally incapacitated for work. Heavy glycosuria and acidosis were present at home until March, 1920. During this time two attempts were made to control the sugar by fasting and low diet, but glycosuria was not completely abolished at any time.

In March, 1920, he entered a government hospital, where he remained until his discharge in August, 1920. His diet averaged about 1500 calories, and during the first 4 months of his hospital treatment he was free of glycosuria the greater part of the time, with the aid of fast-days. The blood sugar ranged from 0.200 to 0.340 per cent. Edema developed during this period. He lost in strength and weight. Glycosuria became constant and uncontrollable in June, and symptoms of acidosis developed.

Following his admission to the Institute, the existing heavy glycosuria and acetonuria cleared up as usual with undernutrition, but trivial quantities of food then served to bring a return of sugar. The effect of undernutrition in building up tolerance is well illustrated in this case. A diet of only 40 gm. protein was continued for 20 days. The diet subsequently was increased very slowly, and consisted chiefly of protein for maintaining strength, while the low calories reduced the body weight from 111 lb. at admission to 81 lb. at discharge. By this means, during 11 months of treatment in the Institute, the tolerance was built up so that a very satisfactory diet for such a patient, namely, 65 gm. protein, 20 gm. carbohydrate and 1600 calories was assimilated with constantly normal plasma sugar. The patient was capable of light activities all day long, and could take walks of a mile or two, but was not fit for work or self-support. After discharge, he remained symptom-free on careful diet for about a year, then abandoned treatment on a quack promise of cure, and thereafter went rapidly from bad to worse and gave up hope. His psychic makeup has always been rather delicate. He was ordinarily faithful to treatment, but on several occasions wandered away with no definite destination and ate to excess.

His family brought him back to the Institute on Sept. 12, 1922, entirely on the hope of insulin treatment. Coma was impending. Glycosuria and acetonuria were heavy, the plasma sugar was 0.652 per cent., and the plasma bicarbonate 21.4 vol. per cent. Even with the acidosis, the apparent gain of weight to 102 lb. was due to marked edema. Sufficient insulin was not immediately available, and accordingly the patient was given a strictly fat-free diet of 25 gm. protein and 15 gm. carbohydrate, with first 15 and later 5 gm. of sodium bicarbonate per day. In this way by Sept. 16 glycosuria and acetonuria were much diminished, the plasma sugar was reduced to 0.405 per cent., and the plasma bicarbonate raised to 72.9 vol. per cent. Insulin was then begun in dosage of 1 unit daily (½ unit in the morning and ½ unit in the evening), with continuance of the low diet. By this means glycosuria was brought to an end on Sept. 21, and hypoglycemia and slight accompanying symptoms occurred on Sept. 26. The weight, which had risen as high as 109 lb. through increase of edema, fell rapidly as the edema cleared up under salt restriction. These results were undoubtedly greatly facilitated by the small dose of insulin. The detailed record of the case is given in paper No. 3 (Table 15).

One interesting feature was that when the diet had not yet exceeded 1500 calories, the patient seemed distinctly better and stronger than on his former diet of 1600 calories without insulin. It is conceivable that a more abundant supply of insulin may of itself serve to relieve diabetic asthenia. This result in such a patient, however, can best be explained as psychic. In the same way, the patient's mental attitude is better, for the sole reason that he feels the reassurance of a powerful and positive treatment. Nevertheless, he can not be trusted to follow consistently even the most liberal and satisfying diets. After long periods of fidelity, he still breaks restraint occasionally, and immediately feels remorse and confesses. The consequences of such lapses are less serious and more quickly controlled by means of insulin treatment.

The physical signs in the chest were suspicious from the time of the first admission, but nothing positive could be established, and repeated sputum examinations were negative. Recently tubercle bacilli have appeared in the sputum, positive signs have developed in both lungs, and a slight evening rise of temperature occurs frequently. The diet was therefore increased to 100 gm. protein, 125 gm. carbohydrate and 2800 calories, with which 54 units of insulin proved to be necessary to prevent glycosuria. The weight was thus raised only to 103 pounds, and appetite and digestion began to fail. The protein and carbohydrate were therefore left unchanged and the fat reduced so as to reduce the total calories to 2500. The general strength is rather poor, and the prognosis doubtful. The only hope, however, lies in the high nutrition which is made possible by insulin.

Case No. 337. (Moderate youthful diabetes. Improved nutrition with insulin after two years of stationary tolerance.) Male. American. Age 18 years. Height 5 feet 6 inches. Weight 120 lb. maximum, 95 lb. at admission, Sept. 14, 1920. Family history negative. Personal history negative except for attacks of tonsillitis every winter up to tonsillectomy five years ago. Only one attack has occurred since. This was in October, 1917, and acute diabetic symptoms appeared one week afterward. The diagnosis was made and treatment begun within a month. The patient was scrupulously faithful to treatment, but had repeated returns of glycosuria requiring progressive reductions of diet, and gradually lost weight and strength. Glycosuria and moderate ketonuria had been present for four months prior to admission. These were cleared up by the usual undernutrition, and the patient was discharged Dec. 21, 1920, on 65 gm. protein, 15 gm. carbohydrate, and 1600 calories, at a weight of 91 lb. He maintained a practically unchanged condition through his careful fidelity, with only occasional tendencies to hyperglycemia. He returned to the Institute Nov. 19, 1922, for insulin treatment, at the identical weight of 91 lb. He was discharged Dec. 21, 1922, with the treatment still incomplete, but with adequate training for the use of insulin at home. The diet has gradually been increased to 80 gm. protein, 45 gm. carbohydrate, and 2000 calories, and the weight has risen to 110 lb., with a corresponding return of almost normal strength.

Only 4 units of insulin per day could be given at discharge, owing to the limited supply. To accomplish the results described, a gradual increase of the dosage to 12 units has been necessary. It was feasible to make these changes entirely on the basis of advice by mail or long distance telephone, because of the high intelligence and trustworthiness of the boy and his family. They had had years of thorough training in diabetic diets, and the boy had both witnessed and experienced hypoglycemic symptoms during his treatment in the Institute. These symptoms appeared on a few occasions at home, but he knew how to check them by taking carbohydrate or reducing insulin. On the other hand, he tested his urine regularly for sugar and could alter his diet or dosage slightly so as to stop glycosuria. At present he is remaining free from

both glycosuria and collapse symptoms, but his plasma sugar is usually close to 0.2 per cent.

Case No. 339. (Mild juvenile diabetes. Improved nutrition with moderate doses of insulin. Different dosage for hyperglycemia and for normal blood sugar.) Female. American. Age 12 years. Height 4 feet 8 inches. Weight 80 lb. maximum, 72 lb. at admission, September 15, 1920. Family history negative. Personal history—diarrhea in first and second summers, measles and chickenpox at 9 and 10 years. At 11½ years (February, 1920) she had acute abdominal pain, nausea and vomiting, without fever, and was well within 24 hours. Ten days later she developed typical bilateral mumps, with normal recovery and with negative urinalyses. In June, 1920, polyuria and enuresis appeared, but the urine was again reported sugar-free. In August, extreme thirst and polyuria appeared, and glycosuria was found and yielded only partially to the diets employed.

The case proved to be mild, and the diet was quickly built up to 60 gm. protein, 15 gm. carbohydrate, and 1600 calories. Hyperglycemia was kept absent at home for a year, but slight difficulties then required a reduction to 1400 calories. The child looked in perfect health and did everything that normal children do. She was readmitted Sept. 25, 1922, for trial of insulin in a mild case.

The height was then 4 feet 9 inches, and the weight still 72 lb. With only 1 unit of insulin per day, it became possible from Sept. 28 to Nov. 1 to omit the usual weekly days of partial fasting. This was equivalent to an increase of the diet by approximately one-tenth, but the original plasma sugars of 0.106 and 0.107 per cent. gradually increased to 0.168 per cent. as the weight gradually rose to 76 lb. The plasma sugar was only partially reduced by an increase of insulin to 2 units, and a return to the normal level required 4 units per day. This is an instance in which the difference between hyperglycemia and normal blood sugar could apparently be measured in units of insulin. Beginning Nov. 16, the diet was increased to 65 gm. protein, 25 gm. carbohydrate, and 1500 calories. With the same dosage of insulin, the plasma sugar gradually rose from 0.120 per cent. to 0.157 per cent. at discharge on Nov. 23, at the weight of 76 lb. At home the hyperglycemia increased above 0.2 and then above 0.3 per cent. and glycosuria appeared notwithstanding gradual increase of insulin. Dosage of 12 units, divided in two injections per day, has finally become necessary to reduce the plasma sugar to 0.140 per cent., at a weight of 78 lb. The child is obviously stronger and better nourished than before, and the parents are much less worried.

Case No. 356. (Diabetes with middle ear and mastoid infection.) Male. Hebrew. Age 33 years. Height 5 feet 4 inches. Weight 168 lb. maximum, 115 lb. at admission, Oct. 18, 1920.

Family and personal history negative. The onset of diabetes was acute in July, 1918, with polyuria, polydipsia and polyphagia. Within 4 weeks his weight dropped from 150 to 130 lb. Diagnosis was made six weeks after onset. On close restriction of carbohydrate, glycosuria was reduced to traces within 5 weeks, but never entirely cleared. He became

dissatisfied with the diet treatment, tried numerous quack remedies, and steadily lost weight and strength.

On Oct. 18, 1920, he was admitted to the Physiatric Institute, where he was treated one month. Glycosuria persisted for three days on a diet of only 30 gm. protein, and two weeks were required to reduce the blood sugar to normal. He was faithful to diet. After returning to his home in care of an experienced dietitian, his tolerance increased within six weeks to 60 gm. protein, 15 gm. carbohydrate and 1400 calories. He made a few office calls, but later abandoned treatment.

He was not seen again until Oct. 18, 1922, when he again entered the Institute. Since his previous discharge he had lost weight, and on several occasions was drowsy with acidosis. In June, 1922, he had gone to Carlsbad for treatment, where he did not become sugar-free but developed a middle ear abscess which was very painful and discharged continuously for 2 months. He returned to America about Oct. 8, and just before arriving in New York had severe pain in the left ear and mastoid region accompanied by fever, chills and sweating. Upon arrival at the Institute he was very weak and emaciated, and weighed only 98 lb.

Physical examination—Emaciated, weak, adult male of small stature. He is in bed the greater part of the time, is fatigued, shows evidence of loss of sleep, and is in acute distress with pain in the left ear. Eyes, nose and throat normal. The left ear is edematous and red about the meatus. There is slight eczema of the canal. The drum is perforated and shows old scarring, and numerous granulations in the middle ear. Redness, swelling and tenderness are present over the mastoid region, with excruciating pain on pressure over that region. Urine shows heavy glycosuria, but only faint nitroprusside test. Plasma sugar 0.469 per cent.

On account of the patient's poor condition, operation for mastoiditis was deferred. He was placed on a low diet of 25 gm. protein and 15 gm. carbohydrate, but response to treatment was slow, glycosuria continued heavy, and the plasma sugar decreased only from 0.469 to 0.341 per cent. after four days. During this interval there was little advance in the mastoid condition, but there was considerable pain which was controlled by morphine. On the fifth day after admission, Oct. 23, mastoidectomy was performed uneventfully under ether anesthesia. For two weeks afterward, glycosuria was heavy on a diet of 40 gm. protein and 10 gm. carbohydrate. There was considerable discharge from the wound, but healing progressed normally. On Nov. 8, insulin was administered in doses of 2½ units twice a day, and the diet was increased to 55 gm. protein, 15 gm. carbohydrate and 700 calories. The severity of the case is shown by the fact that glycosuria could not be controlled until the dosage was increased to 16 units, as shown in Table 2. Further increases were made so that at discharge on Dec. 30 he was taking 90 gm. protein, 25 gm. carbohydrate and 1800 calories, with 21 units of insulin daily. The mastoid wound healed normally and rapidly. The weight had risen to 96 lb., and the strength had increased so that he was able to return to work.

In February, 1923, patient relaxed diet, abandoned insulin treatment, and ceased to report for office calls or examinations. Glycosuria was then constant. He carried on light work in his office, but his strength

TABLE 2
Case No. 356

Date 1922	Diet			Urine		Plasma Sugar Mg. Per 100 cc.	Insulin Units Per Day	Body Weight, Lb.
	P. Gm.	F. Gm.	C.H. Gm.	Qualitative Glucose	Nitroprusside			
Oct.								
19	27	11	5	++++	++	469	..	98
20	25	0	15	++++	++	385	..	..
21	25	0	15	++++	++	...	..	..
22	25	0	15	++++	+	341	..	..
23-31	40	0	10	++++	++	...	..	..
Nov.								
1- 4	40	0	10	++++	++	...	..	..
5- 7	15	0	25	++++	++	...	..	..
8-10	55	46	15	++++	++	405	5	95
11-13	55	46	15	+++	++	349	8	93
14-15	55	46	15	++++	+++	357	8	98
16-18	55	46	15	++++	++	385	8	98
19-26	55	46	15	+++	++	341	12	95
27	55	57	15	+++	+	268	16	97
28-30	55	46	15	+	+	...	16	93
Dec.								
1-2	40	18	15	+	0	171	16	97

and general condition gradually grew worse. A telephone communication from his wife on April 16 stated that he was suffering from pleurisy and cough, which had been present for two weeks. He had lost 5 pounds in weight, and was making no attempt to control his condition. The case shows that some patients will still refuse to submit to the inconvenience of treatment, even under the remarkably favorable conditions created by insulin.

Case No. 396. (Disability out of proportion to severity of diabetes. Restoration of usefulness by insulin.) Male. American. Age 56 years. Height 6 feet. Weight 236 lb. maximum, 186 lb. when first seen in November, 1920. Family and personal history unimportant. Diabetes was very recently diagnosed but has probably been of some years' duration. Treatment was carried out at home under a highly competent nurse, and by ordinary standards the severity of the case was only moderate and the results were satisfactory. It was possible up to November, 1922, to maintain undiminished tolerance for 80 gm. protein, 60 gm. carbohydrate and 2800 calories, and a body weight of 180 lb. The case was unique in that this relatively liberal diet reduced the patient to a state of morbidness and semi-invalidism. He had been accustomed to large eating and large expenditure of energy, due partly to his height and large frame

and partly to his great activity. He was scrupulously faithful in diet and had no complaints of hunger, but apparently could not adjust himself to the lower level of energy and continually felt mentally and physically unfit. He was selected among the small group for early trial of the effects of insulin in relatively mild cases, and accordingly began to receive the treatment in November, 1922. The dosage at first was only 2 units per day, and with a slow increase to 6 units there was still no important result. With larger supplies of insulin, it has become possible to increase the dosage to 24 units per day, and the diet to 100 gm. protein, 100 gm. carbohydrate and 3500 calories. The patient now holds a stationary weight of 190 lb., and his physical and mental condition is transformed. He has become cheerful, active and able to carry on his business affairs. This effect is not psychic, as it was absent during the first few months of low dosage and has become evident only in parallel with the increase of diet and weight. Both hyperglycemia and a slight staphylococcal infection of the nose have lately been brought under satisfactory control.

Case No. 465. (Severe juvenile diabetes. Partial improvement with small doses of insulin. Discontinuance of insulin treatemnt.) Female. Jewish-American. Age 11 years. Height 4 feet 10 inches. Weight 68 lb. before diabetes, 58 lb. at admission, February 17, 1921. Family history negative, except that the patient's only brother died in diabetic coma at 2½ years. Personal history practically clear except for influenza in 1919. Diabetes may have begun shortly afterward, as there has been gradual loss of weight, but the first diagnosis was made two days before admission, when a physician was consulted on account of weakness, anorexia and vomiting.

At admission, there was heavy glycosuria but not a dangerous degree of acidosis. The symptoms were quickly controlled by undernutrition and the diet built up to 60 gm. protein, 35 gm. carbohydrate, and 1700 calories. It was possible to discharge the child at an increased weight of 65 lb., due partly to invisible water retention. She continued in highly satisfactory condition at home for over a year, until the tolerance was seriously damaged by an attack of influenza. After continued difficulties in suppressing glycosuria or hyperglycemia on reduced diets at home, she was readmitted Nov. 14, 1922, with a view to insulin treatment. The weight was 55 lb. and the patient was much weaker than formerly.

Moderate glycosuria and ketonuria persisted during the week Nov. 15-22 on a diet of 45 gm. protein, 10 gm. carbohydrate, and 800 calories. On Nov. 23, 4 units of insulin stopped the glycosuria within 24 hours, and by Nov. 25 the plasma sugar on this dosage had fallen from 0.326 to 0.127 per cent. With gradual increases of diet, it was possible to discharge the patient Dec. 17, 1922, on 60 gm. protein, 20 gm. carbohydrate, and 1200 calories, free from glycosuria but with hyperglycemia of 0.209 per cent., on the same dosage of 4 units of insulin divided in two injections daily. The rising blood sugar and occasional glycosuria were controlled at home only by an increase of insulin to 8 units daily. The weight has not risen above 60 lb. Though there was decided improvement, the parents wrote on Jan. 17 that the patient wished to stop the

injections because of their painfulness and to return to the former diet treatment. They probably do not realize how low the tolerance has fallen, and will probably be compelled to resume insulin treatment before long. This is the only instance in which a patient, especially of the severe type, has chosen to discontinue the use of insulin.

Case No. 518. (Juvenile diabetes, progressing from mild to severe state with violations of diet. Incidental observation of insulin requirement for fat. Improvement in condition and fidelity.) Male. American. Age 3 years. Height 3 feet 4½ inches. Weight 42 lb. maximum, 40 lb. at admission, April 2, 1921. The family history was negative. The boy was unusually rugged and healthy, free from colds and all other illnesses, but inclined to slight obesity. Six days before admission, he suddenly vomited a live worm about 3 inches long. A physician was called, who noticed acetone on the breath and therefore tested the urine, which was found heavy with sugar. Carbohydrates were restricted and the patient referred to the Institute. The condition was easily and quickly controlled, and after discharge normal plasma sugars continued at home on a diet of 65 gm. protein, 30 gm. carbohydrate and 1450 calories, except on a few occasions when diet was broken.

Because of this difficulty, he was again treated in the Institute in April, 1922, but on returning home violated his diet almost constantly. He was finally brought back to the Institute Oct. 14, 1922, with heavy glycosuria and acetonuria, weighing 37 lb. After a week of low diet, he tolerated 40 gm. protein, 15 gm. carbohydrate and 700 calories with normal plasma sugar of 0.105 per cent., but increase of fat to make 800 calories produced hyperglycemia of 0.203 per cent. within five days. Insulin treatment was begun under these circumstances Nov. 6.

Dosage of 2 units per day reduced the plasma sugar to 0.138 per cent., i.e., the two units apparently provided for the assimilation of the 100 calories of added fat. The diet and dosage were gradually increased, until the boy was discharged Dec. 15, 1922, weighing 38 lb., and free from both glycosuria and hyperglycemia on 40 gm. protein, 15 gm. carbohydrate, 1600 calories, and 6 units of insulin per day. A change was made on Jan. 9 to 45 gm. protein, 20 gm. carbohydrate and 1500 calories. Violations of diet have been avoided because the patient is better satisfied with the higher diet and his parents are impressed with the need of care while using insulin. As the body weight has gradually increased to 45 lb., it has become necessary gradually to increase the insulin to 21 units per day, in order to keep glycosuria absent. The height is 3 feet 7 inches, the same as at the second admission in April, 1922. The boy appears like a thoroughly healthy child in all respects and will probably proceed to grow again.

Case No. 526. (Moderately severe diabetes with pneumonia, pleurisy and acidosis.) Male. American. Age 48 years. Height 5 feet 9 inches. Weight 177 lb. maximum in 1910, 135 lb. at admission, April 4, 1921. Father, aged 73, has mild diabetes. Mother, also 73, has arthritis. Personal history—scarlet fever 25 years ago. Numerous attacks of tonsillitis between the ages of 10 and 35 years. Between 1909 and 1911, four attacks

TABLE 3

Case No. 526

Date	Diet				Glycosuria Gm.	Nitroprusside	Blood Plasma			Insulin, Units	Remarks
	P. Gm.	F. Gm.	C.H. Gm.	Total Cal.			Sugar Mg. Per 100 cc.	Total Acetone Mg. Per 100 cc.	CO_2 Cap. Vol. %		
1922 Nov.											
5	...	...	10	...	++++	++++	385	153	60.5	5	8 p.m., fever and impending coma.
	...	...	24	...	.....	....	....	....	....	10	10 p.m.
	...	...	24	...	++++	++++	326	92	73.9	..	11 p.m.
	...	...	...	...	40.00	....	...	....	....	15	12 p.m.
6	...	...	12	...	+	+	...	....	....	..	2 a.m., pain in chest. Consolidation of right lower lung. Temperature, 101.8 F.
	...	...	12	...	.....	....	...	....	....	..	3 a.m.
	...	...	...	...	0	0	234	62	86.8	12	6 a.m., acidosis symptoms relieved.
	...	...	...	...	.....	....	209	....	....	..	8 a.m.
	10	...	10	...	0	+	...	....	....	..	12 m.
	10	...	10	...	36.00	++	...	....	....	4	5 p.m.
7	60	53	20	800	73.39	++	334	....	....	8	Temperature 101 F. Hemoptysis.
8	"	"	"	"	68.40	++	366	....	....	16	" 101 F. Respirations 24.
9	"	35	60	"	78.77	++	...	....	63.3	28	" 101 F. " 24.
10	"	"	"	"	64.08	++	306	59.5	....	40	" 102 F. " 22.
11	"	"	"	"	75.60	++	...	....	....	40	" 98 F. " 24.
12	"	"	"	"	47.61	+++	416	67.2	....	40	
13	"	"	"	"	24.79	....	...	....	....	48	
14	"	"	"	"	7.32	++	326	....	....	48	
15	"	"	"	"	2.47	....	211	....	....	48	
16	"	"	"	"	0	0	195	....	....	48	
17	"	"	"	"	7.38	....	319	....	....	48	

18	"	"	"	"	6 42	+	...	....	....	48
19	60	68	60	1100	+	....	...	....	....	48
20	"	"	"	"	+	+	268	....	....	48
21	"	"	"	"	+	....	...	....	....	36
22	"	"	"	"	10 95	+	312	....	....	36
23	"	"	"	"	14 75	....	....	....	....	48
24	"	"	"	"	+	0	...	....	....	48
25	"	"	"	"	0	0	...	....	....	48
26	"	"	"	"	0	0	214	....	60 0	36
27	"	"	"	"	0	+	131	....	....	16
28	"	158	"	1902	0	....	178	....	....	16
29	"	"	"	"	0	0	...	....	....	32
30	"	"	"	"	0	+	...	....	....	32
Dec.										
1	"	"	"	"	0	0	...	....	....	28
2	"	"	"	"	0	0	146	....	....	30
3	"	"	"	"	0	+	...	....	....	30
4	"	202	"	2300	+	+	195	....	....	20
5	"	"	"	"	+	0	...	....	....	20
6	"	"	"	"	0	0	270	....	61 0	20
7	"	"	"	"	0	0	...	....	....	20
8	"	"	"	"	0	0	...	....	....	30

of appendicitis. Appendectomy in 1912. The urine at that time was pronounced normal. The onset of diabetes was acute, with polyuria, polydipsia, weakness and loss of weight in July, 1916. A physician 3 weeks later diagnosed diabetes and mild acidosis. The weight had dropped to 141 lb. With bed rest and a diet composed chiefly of protein and green vegetables, glycosuria subsided within a week. He was discharged on an unweighed diet. The urine was tested only occasionally. In June, 1917, symptoms of thirst, weakness and fatigue reappeared. Glycosuria was known to be present the greater part of the time until his treatment in the Physiatric Institute, April 4 to May 1, 1921. His ultimate food tolerance proved to be only 55 gm. protein, 5 gm. carbohydrate and 1200 calories.

He followed diet and remained symptom-free at home until June, 1922, when he became careless and stopped coming for tests.

On November 5, 1922, the patient was seen at his home in consultation on account of acidosis and drowsiness. He had steadily lost weight and strength during the preceding months, and for the past ten days had been short of breath and drowsy. He had understood the seriousness of his symptoms, and attempted to control glycosuria by fasting and large doses of soda, but there was little improvement. During Nov. 4 he slept the greater part of the time, vomited several times and complained of slight headache and loss of appetite.

He was admitted to the Institute at 8 P. M., Nov. 5, 1922. Examination showed impending coma and bilateral lobular pneumonia. Table 3 shows the laboratory findings and treatment. He responded with unusual ease to insulin under the circumstances, perhaps because of the preceding fasting. After only 30 units of insulin on Nov. 5, the urine became free from sugar and acetone on Nov. 6. On this day he was given only 12 units at 6 A. M., with the small quantities of carbohydrate shown, and glycosuria reappeared by 5 P. M.

At noon on Nov. 6 he complained of pain in the right lower chest, and had a hacking cough but no expectoration. Physical examination revealed dullness and moist rales over the lower portion of the right chest in the mid-clavicular line, extending laterally to the mid-axillary line. Breath sounds were harsh and grating. No friction rub was present, but he had acute pain on deep inspiration. Respirations were 20, pulse 84, temperature 101.8. For two days following, he spat up small amounts of blood-tinged sputum. The pain continued until Nov. 10, when the fever fell and resolution began. Sugar was present in the urine, ranging from 36 to 79 gm. per day. Beginning Nov. 13, after all evidences of pneumonia had subsided, 48 units of insulin, in doses of 12 units four times a day, abolished glycosuria and gradually reduced the blood sugar.

The diet was gradually increased to 60 gm. protein, 60 gm. carbohydrate and 2300 calories. He was discharged Dec. 8, 1922, on 60 gm. protein, 60 gm. carbohydrate and 2300 calories, and 30 units of insulin in doses of 10 units three times a day. His weight during treatment in the Institute increased from 125 to 133 lb.

He follows treatment and reports regularly for examinations. He has

remained free from glycosuria the greater part of the time, and has been able to resume full duties as a banker. His protein and carbohydrate have been increased to 100 gm. each, and his insulin doses have varied between 30 and 45 units per day. His present weight is 155 lb., which represents an increase of 30 lb. since his admission.

Under these circumstances he is finding it almost impossible to keep his condition under smooth control. Notwithstanding all arrangements of meals and insulin dosage yet devised, he is liable to have glycosuria at certain times of the day and hypoglycemic symptoms two or three hours later. It will probably be necessary to reduce the diet and the insulin dosage in order to regulate this condition.

Case No. 529. (Juvenile diabetes following infection. Insulin requirement for protein and carbohydrate.) Female. American. Age 10 years. Height 4 feet ¼ inch. Weight 56 lb. maximum, 54 lb. at admission, March 30, 1921. The family history was negative. The patient was entirely healthy until the onset of typoid fever in September, 1919. Abdominal symptoms at this time led to an operation for appendicitis. The appendix was found normal and the diagnosis of typhoid was then made by blood culture. After very severe illness the temperature returned to normal in six weeks. Her weight fell to 40 lb. during the typhoid. During convalescence, she was on a very abundant diet with much carbohydrate, and increased her weight by Dec. 16 to 52 lb. Thirst and polyuria began at this time, and glycosuria was discovered within ten days. This history suggests the possibility of an acute pancreatitis with the typhoid.

Restrictions of carbohydrate and total calories controlled the glycosuria, and it did not return during an attack of scarlet fever in May, 1920. The child lived practically a normal life and attended school. Glycosuria tended to return, and she was referred to the Institute for adjustment of diet. Control of the condition was easy, and she was discharged on a diet of 50 gm. protein, 10 gm. carbohydrate and 1000 calories. There were two subsequent readmissions to the Institute because of minor difficulties with the diet at home. Her fourth admission in January, 1923, was for the purpose of improving her nutritive condition by the use of insulin. Details of this period are given in paper 2 (Table 2).

She was discharged Feb. 18, 1923, with her diet changed to 90 gm. protein, 80 gm. carbohydrate and 1800 calories. The glycosuria on this diet was not abolished by 15 units of insulin, but with 18 units per day she remained sugar-free without difficulty, until the weight reached 54 pounds. The diet has since been raised to 1900 calories by increase of fat only. A rise of weight to 56 pounds has been attended with the usual disproportionate increase of insulin requirement, which is now 36 units per day. The child has become the picture of health, and pictures of her condition before and after insulin treatment would show a miraculous contrast.

Case No. 539. (Moderate juvenile diabetes. Tolerance undiminished with careful diet for one year, lost rapidly with carelessness for seven months. Insulin requirement for carbohydrate. Clinical improvement.)

Female. American. Age 7 years. Height 4 feet ½ inch. Weight 43 lb. before diabetes, 38 lb. at admission, May 22, 1921. Family and personal history entirely negative. The history from her physician was that he had first seen her April 28, 1921, in semi-coma. She had supposedly shown loss of weight and other symptoms for only a few weeks. After recovery from the acute condition, she was referred to the Institute on May 22.

The case proved to be of only moderate severity, and at the time of discharge, July 8, 1921, a diet of 55 gm. protein, 20 gm. carbohydrate and 1300 calories caused only slight hyperglycemia. As a precaution, her allowance at home was only 50 gm. protein, 15 gm. carbohydrate and 1100 calories. The weight was 39½ lb. Improvement continued, and the patient spent ten days in the Institute in December, 1921, purely for observation purposes, arriving with normal plasma sugar and body weight of 46 lb. Subsequently, the parents were encouraged by the child's good health gradually to relax their strictness, and in the course of some months glycosuria returned. The downward progress was then rapid, and the patient was returned to the Institute Feb. 4, 1923, with heavy glycosuria, emaciation and weakness at a weight of 34 lb.

On a diet of 30 gm. protein and 5 gm. carbohydrate, glycosuria of 6 gm. was still present Feb. 9, on which day 4 units of insulin cleared up the sugar within 24 hours. The further record is given in paper No. 2 (Table 16). The present diet is 80 gm. protein, 80 gm. carbohydrate and 1400 calories, with 24 units of insulin given in three doses. The weight has risen to 46 lb., and there has been a still greater gain in strength and spirits. An interesting phase of the case is that this patient, not yet nine years old, will have to go to Cuba and carry most of the responsibility for her own diet and insulin treatment. She seems able to do so with considerable success, and already gives her own insulin injections.

Case No. 574. (Juvenile diabetes. Insulin requirement for fat. Restoration of normal nutrition with insulin.) Female. Jewish-American. Age 2 years 8 months. Height 2 feet 10¾ inches. Weight 30 lb. maximum, 18 lb. at admission, May 16, 1921. The family history was negative. The child had never had the slightest known illness in her life until acute diabetic symptoms developed two months before admission. In the absence of treatment, the weight had fallen with extreme rapidity from 30 lb. to 18 lb. At admission, glycosuria was heavy but ketonuria absent. On a diet of 15 gm. protein and 10 gm. carbohydrate, glycosuria ceased on the second day, and the plasma sugar three days later was 0.117 per cent. The patient was discharged June 25 with the same plasma sugar, weighing 17 lb., on a diet of 35 gm. protein, 10 gm. carbohydrate and 450 calories.

Favorable progress at home permitted gradual increase of the diet to 40 gm. protein, 20 gm. carbohydrate and 800 calories, with the usual day of partial fasting each week. By January 1, 1922, the weight had increased to 22 lb. and the general condition was excellent. In January she had mumps in severe form; glycosuria required sharp reduction of the

diet, and the tolerance was damaged so that subsequently no more than 20 gm. protein, 5 gm. carbohydrate and 350 calories could be tolerated. She was readmitted to the Institute August 2, 1922, and normal plasma sugars were maintained on this diet to August 16.

Beginning August 17, the diet was increased to 60 gm. protein, 60 gm. fat, 6 gm. carbohydrate and 804 calories, preparatory to insulin treatment. Glycosuria appeared within 24 hours, and increased steadily to 15.3 gm. on August 22. On this day 1 unit of insulin abolished the glycosuria completely. With 2 units daily (1 unit night and morning) the plasma sugar was reduced to 0.098 per cent. by the evening of August 29. Substitution of salt solution on August 31 resulted in a prompt return of hyperglycemia. The early effects upon the plasma sugar are shown in table 25 (page 949). Further details are given in paper No. 3 (Table 5). The patient was discharged March 11, 1923, free from glycosuria with 15 units of insulin, on a diet of 65 gm. protein, 60 gm. carbohydrate, and 1000 calories, at a weight of 28 lb. Her appearance and behavior are those of a normal child.

Case No. 755. (Moderately severe diabetes. Insulin requirement for carbohydrate, protein and fat.) Male. American. Age 44 years, Height 5 feet 11 inches. Weight 150 lb. maximum, 118 lb. at admission, July 6, 1921. Family history—father and mother are obese. No diabetes in family. Personal history—measles, whooping cough, scarlet fever, typhoid. Apparent onset of diabetes was indicated by polyuria and weakness 14 months ago. After treatment in a sanatorium, he remained sugar-free on diet for six months, then changed to chiropractic treatment without dietary restrictions and has progressed very rapidly downward. After becoming nearly sugar-free by resumption of medical treatment in June, he came to the Institute for further dietary advice.

The slight glycosuria cleared up in 24 hours, and the plasma sugar became normal in five days. The patient was discharged July 28, 1921, on 55 gm. protein, 10 gm. carbohydrate, and 1400 calories, at a weight of 115 lb. On returning to his home in the south, he was faithful in intentions but inaccurate in his diet, and glycosuria gradually returned. In attempting to prevent loss of weight by eating more, he lost more rapidly, and was discouraged until he heard reports of the discovery of insulin. He was readmitted for this treatment Jan. 14, 1923.

At this time his weight was 105 lb., and ketonuria was present as well as heavy glycosuria. After one week of a diet limited to 30 gm. protein and 5 gm. carbohydrate, glycosuria was rapidly diminishing but still amounted to 14.9 gm. in 24 hours, and the plasma sugar had fallen from 0.416 to 0.349 per cent. With 2 units of insulin, the glycosuria ceased within one day and the plasma sugar in one week fell to 0.081 per cent. The detailed record is given in paper No. 2 (Table 6). The patient is still under treatment, and is taking 16 units of insulin divided in two injections per day, which keeps him free from glycosuria and with nearly normal blood sugar on a diet of 100 gm. protein, 100 gm. carbohydrate, and 2000 calories. His weight has risen to 115 lb., and his strength is rapidly improving.

Case No. 783. (Severe diabetes. Stationary progress on low diet for 1½ years. Insulin requirement for carbohydrate and protein. Improved nutrition.) Female. American. Age 22 years. Height 5 feet 5 inches. Weight 133 lb. maximum, 87 lb. at admission, July 25, 1921. Family history negative. Personal history—whooping cough, measles, chickenpox in childhood. Diabetes began with thirst and polyuria in 1912. The diagnosis was delayed some months, but during the remainder of the nine years she has followed diet faithfully. The diet at first was liberal but was gradually reduced with successive returns of glycosuria. She was referred to the Institute because glycosuria was finally present on diets of 500 calories or less, which were too low to support life.

At admission, the urine contained only a trace of sugar on account of the extremely low recent food intake, but the plasma sugar of 0.260 per cent. explained why additions to the diet had always given rise to glycosuria. A semi-fasting program up to Aug. 14 reduced the weight to 85 lb. and the plasma sugar to 0.117 per cent. It then became possible to maintain normal plasma sugar while gradually building up a diet of 55 gm. protein, 15 gm. carbohydrate and 1000 calories, on which the patient was discharged Sept. 8, 1921, weighing 81 lb.

At her western home, though very thin, she went on with her studies and graduated from University, and since has been perpetually busy with various studies and philanthropic work. She was nominally living on 700 calories throughout this time, but not enough allowance was made for various bulky foods used, so that the actual ration was probably up to 1000 calories. The treatment was scrupulously controlled with blood and urine analyses by her local physician, and the tolerance evidently remained unchanged. She was readmitted Jan. 23, 1923, still active and energetic at a weight of 82 lb., and tolerated her former diet of 55 gm. protein, 15 gm. carbohydrate and 1000 calories up to Jan. 28 without difficulty. Beginning Jan. 29, an increase to 60 gm. protein, 25 gm. carbohydrate and 1200 calories produced hyperglycemia of 0.294 per cent. and glycosuria of 6.24 gm. on the second day, indicating the impossibility of exceeding the established limits of diet.

Without change in the diet, 4 units of insulin stopped the glycosuria within 24 hours. The record with insulin treatment is given in paper No. 2 (Table 17). The patient was discharged April 10, 1923, on a diet of 100 gm. protein, 100 gm. carbohydrate and 2000 calories. Daily dosage of 20 units of insulin, divided in three injections daily, permitted the assimilation of this diet without glycosuria but with well-marked hyperglycemia. The weight has risen only to 88 lb., the slow apparent increase being probably accounted for by replacement of water with fat. The strength has increased disproportionately, and it is anticipated that the patient will be equipped for any activities she may care to pursue.

Case No. 787. (Moderate diabetes, with suspicion of tuberculosis. Downward progress estimated in terms of insulin. Insulin requirement for increased diet. Influence of exercise. Improved prognosis.) Male. American. Age 43 years. Height 6 feet. Weight 229 lb. maximum, 179 lb. at admission, July 30, 1921. Family history negative except for obes-

ity in mother and three sisters, and tuberculosis in one brother. Personal history negative except for measles and rheumatism in childhood. Duration of diabetes unknown. "Autointoxication" was diagnosed two years ago. The entire loss of weight is supposed to have occurred within the past year. He entered the Institute because diet treatment at home had not controlled the glycosuria.

Mild bronchitis was present at admission, and tuberculosis was suspected by the family physician and suggested by physical and X-ray examinations, but no positive diagnosis was made. Another suspicious feature was that the mild appearing case was unusually difficult to control. After three weeks of a diet of 40 gm. protein and 10 gm. carbohydrate, it became possible gradually to build up the allowance to 75 gm. protein, 20 gm. carbohydrate and 1600 calories, on which the patient was discharged Sept. 30, 1921, at a weight of 147 lb. He was definitely weaker than at admission but had reasonable strength and all active bronchitis had cleared up. Diet was followed at home for nearly a year, though hyperglycemia was unusually difficult to prevent. The patient gradually became careless and for several months was under no observation and ate without much restraint.

He was readmitted Jan. 29, 1923, weighing 146 lb., and with heavy glycosuria and slight ketonuria present. On a diet of 60 gm. protein, 30 gm. carbohydrate and 1600 calories up to Feb. 14, approximately 12 units of insulin per day was required to prevent glycosuria, with hyperglycemia present. It can be estimated, therefore, that the loss of tolerance in this case since the first admission amounted to approximately 12 units per day in terms of insular function.

The table illustrates the manner in which the insulin requirement rises with increase of total diet and body weight. The relatively small part played by the mere increase of the glucose value of the diet is exemplified by the increase of carbohydrate and protein, beginning March 18. As the fat was reduced so as to keep the total calories unchanged, it will be observed that no perceptible effect upon the urine or blood sugar was produced by this alteration.

The patient ordinarily exercised vigorously by walks of five to ten miles daily. It was suspected that the isolated outbreaks of glycosuria on March 16 and 20 were due to reduction of this exertion.. Accordingly, on March 24, 25 and 26 the patient by request remained quiet in his room, occupying himself only with reading and writing. For the several days preceding and following this period he exercised even more strenously than usual. No effect was noticeable until the third rest day, March 26, when glycosuria of 16.4 gm. suddenly appeared. Glycosuria and marked hyperglycemia continued through March 27 and 28, while the patient was walking to the limit of comfortable endurance. Everything cleared up, however, on March 29 and 30 with continuance of the exercise. It appeared, therefore, that the effects of rest or exercise were slow in manifesting themselves, but yet the outbreak of sugar seemed to be definitely due to the experimental rest period. Exercise therefore apparently tends to improve assimilation with insulin treatment, as has been known heretofore with diet treatment.

TABLE 4
Case No. 787

Date 1923	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Feb.								
1	60	137	30	1600	++++	455	146	2
2	"	"	"	"	++++	405	...	2
3	"	"	"	"	58.58	...	140	2
4	"	"	"	"	26.18	...	...	4
5	"	"	"	"	11.20	349	...	4
6	"	"	"	"	19.24	...	...	4
7	"	"	"	"	21.28	357	144	4
8	"	"	"	"	6.97	...	...	8
9	"	"	"	"	3.20	...	146	8
10	"	"	"	"	4.86	258	...	8
11	"	"	"	"	0	...	...	12
12	"	"	"	"	0	200	145	12
13	"	"	"	"	0	...	...	12
14	"	"	"	"	0	...	146	12
15	80	166	45	2000	0	...	...	12
16	"	"	"	"	0	...	...	12
17	"	"	"	"	22.05	...	...	12
18	80	215	60	2500	37.60	326	147	12
19	"	"	"	"	30.25	...	148	12
20	"	"	"	"	15.11	...	...	12
21	"	"	"	"	45.44	...	...	16
22	"	"	"	"	65.12	...	...	16
23	"	"	"	"	42.94	...	...	16
24	"	"	"	"	33.84	334	...	16
25	"	"	"	"	33.30	349	...	20
26	"	"	"	"	34.32	...	144	20
27	"	"	"	"	19.46	...	...	20
28	"	"	"	"	13.65	...	144	30
Mar.								
1	"	"	"	"	23.50	385	...	30
2	"	"	"	"	28.49	...	...	30
3	"	"	"	"	17.82	...	...	30
4	"	"	"	"	23.74	...	146	36
5	"	"	"	"	23.63	375	...	36
6	"	"	"	"	10.40	334	147	36
7	"	"	"	"	13.42	...	...	36
8	"	"	"	"	+	...	148	45
9	"	"	"	"	+	...	...	45
10	"	"	"	"	+	238	...	45
11	"	"	"	"	0	...	...	36
12	"	"	"	"	+	...	151	36
13	"	"	"	"	0	...	150	36
14	"	"	"	"	0	214	...	36
15	"	"	"	"	0	...	153	36
16	"	"	"	"	8.73	...	...	36
17	"	"	"	"	+	...	153	36
18	100	189	100	2500	+	...	...	36
19	"	"	"	"	0	...	...	36
20	"	"	"	"	8.00	...	155	36
21	"	"	"	"	0	268	...	36
22	"	"	"	"	0	...	153	36
23	"	"	"	"	0	...	...	36
24*	"	"	"	"	0	...	157	36
25*	"	"	"	"	0	184	157	36
26*	"	"	"	"	16.40	...	...	36
27	"	"	"	"	26.80	349	153	36
28	"	"	"	"	9.30	375	...	36
29	"	"	"	"	0	...	156	36
30	"	"	"	"	0	234	...	36

*Rest day.

The patient was discharged March 31, free from glycosuria on the diet and insulin dosage shown, at a weight of 156 pounds.

If the suspicion of tuberculosis be well founded in this case, there is abundant evidence that high diets producing active diabetic symptoms would result in the most rapid progress of both the tuberculosis and the diabetes and the earliest disability and death. Limitation of diet to the extent necessary to control the diabetes has been the most effective means heretofore for improving the resistance of diabetic patients to tuberculosis and all other infections. Everybody has recognized that the necessity for undernutrition has been one of the handicaps in combating tuberculosis under these conditions, and one of the greatest advantages of insulin must therefore consist in the improved nutrition which is made possible in these combined cases. This patient's general condition is so good that on a higher nutritive plane he should probably have little difficulty in overcoming any slight pulmonary infection which may be present.

Case No. 806. (Moderate juvenile diabetes. Quantitative insulin dosage in relation to glycosuria resulting from carbohydrate and fat respectively.) Female. American. Age 7 years. Height 4 feet and ½ inch. Weight 50 lb. maximum, 40 lb. at admission, August 10, 1921. The only diabetes known in the family was in a paternal grandmother, but when the child's parents were given test doses of 100 gm. glucose the father proved normal and the mother showed marked hyperglycemia and glycosuria. At the age of 2, the patient had a five-day illness diagnosed as "intestinal poisoning." She had measles within the same year, and tonsillitis occasionally up to tonsillectomy in December, 1920. The mother states that there have been constant complaints of fatigue since that operation. Loss of weight was noticed in June, 1921, followed by thirst and polyuria in July, together with loss of appetite and abdominal cramps. Specimens of urine were reported normal by a commercial laboratory at the end of July, and the diagnosis was only made by a consulting physician on the day before admission.

Coma was impending at admission, but cleared up on the usual treatment with fruit juices, fluids and bicarbonate. After a diet limited to 50 gm. carbohydrate for five days to clear up ketonuria completely, two days of lower diet resulted in normal plasma sugar. The patient was discharged with normal blood and urine Sept. 30, 1921, weighing 37 lb. on a diet of 55 gm. protein, 15 gm. carbohydrate and 850 calories. This condition was maintained at home except for occasional errors of diet. At one of these times, Dec. 29, 1922, she was returned to the Institute with traces of glycosuria present to receive insulin treatment.

The detailed record is given in paper No. 2 (Table 18). At the time of discharge, March 1, 1923, the diet was 70 gm. protein, 70 gm. carbohydrate, and 1500 calories, and the insulin dosage was 15 units divided in three injections per day, at a weight of 44 lb. Glycosuria was present on this program, and at home a change has been made to 60 gm. protein, 60 gm. carbohydrate and 1400 calories, with 18 units of insulin. With the high diet, the child is very greatly improved in looks and actions, but

there is difficulty in devising an arrangement which will keep glycosuria consistently absent. Further adjustments will probably be necessary.

Case No. 823. (Severe diabetes with tendency to sharp fluctuations of blood sugar. Insulin requirement for fat and carbohydrate. Improved nutrition, probably an aid to fidelity. Photographs: Figures 5 and 6 before insulin, Figures 7 and 8 after insulin.) Male. American. Age 25 years. Height 5 feet 7 inches. Weight 122 lb. maximum, 89 lb. at admission, August 17, 1921. The family and personal history were unimportant. There was a typical diabetic history of ten months.

The heavy glycosuria, acidosis and lipemia cleared up with three days of 30 gm. protein and 15 gm. carbohydrate, and three more days of only 25 gm. protein. The plasma sugar became normal within the next few days, and the diet was rather rapidly built up to 70 gm. protein, 30 gm. carbohydrate and 1800 calories. The patient was dismissed November 8, 1921, in good condition at a weight of 110 lb.

There were three subsequent admissions between December, 1921, and May, 1922, for short periods, all resulting from dietary experiments on the part of the patient, who was always trying to extend or vary his diet. Each relapse was followed by building up of tolerance at the price of body weight, and the progress was rather rapidly downward.

This was one of a rare type of diabetic cases in which the blood sugar is extraordinarily labile. In a relapse, for example, this patient might have a plasma sugar of 0.536 per cent. and corresponding glycosuria, and 48 hours of semi-starvation might result in a plasma sugar of 0.088 per cent. His blood sugar under treatment was almost uniformly below 0.1 per cent., but a very slight excess of any kind of food over his tolerance gave rise within one or two days to great hyperglycemia and glycosuria. Ordinarily he was vigorous and energetic, but with undernutrition his plasma sugar could quickly be reduced to 0.06 per cent., and with this condition he was weak and depressed. In clearing up glycosuria by a two-day fast at home on his own volition, he once produced a state of rather serious collapse and had to be warned against such undertakings. His reaction to insulin was therefore a matter of some interest, but though the fluctuations of plasma sugar have continued, no special dangers from hypoglycemia have been encountered.

On his fifth admission with glycosuria, October 23, 1922, it was possible to build up the diet rapidly to 65 gm. protein, 35 gm. carbohydrate and 1500 calories for the period November 1 to 4, with normal plasma sugar of 0.108 to 0.112 per cent., but this was at a reduced weight of 85 lb. An increase of fat to make 1800 calories on November 5 raised the plasma sugar to 0.230 per cent. on the following morning. Insulin was then begun in 1 unit dosage, but hyperglycemia persisted and a gradual increase to 4 units failed to prevent glycosuria during the week November 12-19. During the following two weeks, 6 units of insulin was established as the quantity required for assimilation of the extra 300 calories of fat with normal urine and blood.

An addition of 30 gm. carbohydrate was then made, raising the diet to 65 gm. protein, 65 gm. carbohydrate and 1920 calories. The plasma sugar

just preceding this change was 0.129 per cent., and during the following three weeks no change whatever resulted, except that the plasma sugar ranged between 0.145 and 0.160 per cent., with no apparent tendency to rise higher.

The patient was discharged December 21, 1922, on his 1920 calories, with 6 units of insulin, at a weight of 93 lb. His usual practices resulted in a recurrence of heavy glycosuria, and he returned for his sixth admission January 10, 1923. With his body weight the same or a few pounds lower than before, heavy glycosuria was found to persist with the 6 units of insulin and a reduced diet of 55 gm. protein, 25 gm. carbohydrate and 1100 calories. A marked and rapid loss of tolerance thus seems to be indicated as the result of active diabetes notwithstanding the use of insulin.

Details of the last admission are given in paper No. 3 (Table 3). The diet has gradually been increased to 55 gm. protein, 50 to 150 gm. carbohydrate, and 2000 calories, for the assimilation of which 40 to 45 units of insulin per day seems to be required. The plasma sugar remains normal, and there is remarkably little tendency to either glycosuria or hypoglycemia, perhaps because of the stabilizing influence of the fat which composes a high proportion of the diet. The weight has risen to 110 lb. and the strength is increased. With the more liberal diet, it is hoped that the patient's tendency to indiscretions at home may be overcome.

Case No. 839. (Severe diabetes under 18 months' continuous observation. Significance of hyperglycemia and of slight increases of diet illustrated in insulin dosage. Insulin requirements for fat and carbohydrate. Improved nutrition and prognosis.) Female. American. Age 43 years. Height 5 feet 5 inches. Weight 148 lb. maximum, 97 lb. at admission, Sept. 10, 1921. Mother died of tuberculosis, father of diabetes; several brothers and sisters obese. Personal history—measles and whooping cough in infancy; scarlet fever and inflammatory rheumatism at 12; appendicitis and slight endocarditis at 16; typhoid in 1907. Diabetes apparently began in January, 1919, with asthenia. The diagnosis was made a few months later, and undernutrition diets have since kept glycosuria absent except at times when the patient exceeded the quantitative limits. She entered the Institute because of declining weight and strength and difficulty of remaining sugar-free.

At admission, glycosuria was absent, but the hyperglycemia presented unusual difficulties. It was extremely difficult to reduce much below 0.2 per cent. with prolonged undernutrition, but with any increase of diet it quickly rose and led to glycosuria. At the end of March, 1922, it became possible to give a diet of 40 gm. protein, 5 gm. carbohydrate and 1000 calories, at a weight of 82 lb. The patient was up all day and able to attend to various light duties, but nevertheless was a very weak and emaciated invalid. She remained in the Institute until November, 1922, in unchanged condition. The tolerance showed no tendency to rise higher, and perhaps fell slightly with the continuous slight hyperglycemia, for on several occasions reductions of diet as low as 700 calories were necessary to keep the plasma sugar within its usual bounds of 0.150 to 0.175 per cent.

November 6, following one of these reductions of diet, the patient weighed 83 lb., and insulin treatment was begun. The detailed record is given in paper No. 3 (Table 18). It will be noticed that the diet was increased only to 50 gm. protein, 10 gm. carbohydrate and 1000 calories. Nevertheless, the rise of hyperglycemia following this increase was not prevented by 1, 2, or even by 5 units of insulin per day, so that by Nov. 23 the plasma sugar had risen to 0.326 per cent. and glycosuria began. These observations prove that the limits of tolerance defined in the previous prolonged diet treatment were correct, and they give some idea of the extra demand upon the weakened pancreas created even by small additions to the diet. They also make it plain that the slight prolonged hyperglycemia in this case was a genuine indication of a slight overload of the pancreatic function, which might well be expected in the course of sufficient time to cause a gradual breaking down of this function.

After several dietary tests, it may further be noticed that the diet from Jan. 2 to Jan. 10, 1923, was 50 gm. protein, 10 gm. carbohydrate and 1500 calories. Here the increase in glucose value amounted to barely 10 grams above the diet formerly tolerated, and the increase of calories consisted almost wholly of fat. It seems evident that the patient's tolerance had been not below 700 calories or above 1000 calories. Accordingly, the increase of diet represented 500 to 800 calories in excess of the tolerance, and 24 units of insulin per day barely sufficed for the assimilation of this increase without glycosuria but with hyperglycemia. The results of attempts at over-feeding in such a case, especially with high fat diet, are thus clearly shown in terms of pancreatic function. The only defect in this reasoning might be that the patient's tolerance had fallen considerably during the two months of insulin treatment, but such an assumption is not supported by our general experience with insulin.

The patient is still in the Institute. Her highest diet to date has been 60 gm. protein, 100 gm. carbohydrate and 1600 calories. Fifty units of insulin, divided in three injections per day, seemed to be slightly inadequate for the assimilation of this diet, the true requirement being probably about 54 units. The patient has gained weight to 105 lb., and has gained strength to a still greater degree. Her outlook in life is transformed.

Case No. 878. (Severe diabetes, under observation in Institute for 1½ years. Influence of fat, carbohydrate and protein on insulin dosage.) Female. American. Age 47 years. Height 5 feet 7 inches. Weight 126 lb. maximum, 98 lb. at admission, October 12, 1921. Family and personal history unimportant. During the past eight months she has lost weight from 126 lb. to 80 lb., and diabetes was diagnosed at onset of polyphagia and polydipsia four months ago. She was referred to the Institute because of intractable glycosuria and neuritis. The diet was limited to 20 gm. protein daily for seven weeks in order to develop any appreciable food tolerance. A diet of 45 gm. protein, 5 gm. carbohydrate, and 800 calories thus became possible, at a weight of 74 lb. With the patient living continuously in the Institute, a slow steady increase of diet became possible so that by Oct. 12, 1922, she was taking 55 gm. protein, 10 gm.

carbohydrate, and 1500 calories, with increased strength but approximately the same weight. She was merely an emaciated chronic invalid, up and about all day and capable of light exertion and short walks, but with no hope of much further improvement.

November 5, 1922, insulin treatment was begun on the diet mentioned. The detailed record is given in paper No. 3 (Table 6). With an increase of diet to 60 gm. protein, 20 gm. carbohydrate and 1800 calories, increasing insulin dosage up to 6 units daily prevented glycosuria but not hyperglycemia. The allowances have been increased, until recently as much as 120 gm. protein, 200 gm. carbohydrate, and 2640 calories has been taken with 48 units of insulin divided in three injections daily. The weight has risen to 98 lb. The treatment is still incomplete, but the improvement in all respects is very marked.

Case No. 918. (Very severe juvenile diabetes. Transformation of nutritive condition and prognosis by insulin. Difference between hyperglycemia and normal plasma sugar in terms of insulin. Insulin requirement for fat and increased body weight. Photographs: Figures 9 and 10 before insulin, Figures 11 and 12 after insulin.) Female. American. Age 3 years 9 months. Received Jan. 12, 1922, with impending coma. No diabetes, obesity or hereditary disorders were known in the family. The patient had had no illness in her entire life except so-called "cholera infantum," consisting in fever and 6 or 7 liquid bowel movements in each 24 hours for a month during her second summer (1920).

She reached her greatest height of 2 feet 11½ inches and her highest weight of 31 pounds in June, 1921. After only 3 or 4 days of thirst and polyuria, she was taken to the family physician who diagnosed diabetes June 15, 1921. Moderate dietary restrictions kept glycosuria absent most of the time to Aug. 1. On account of weakness, the diet was then increased with protein and fat, keeping the carbohydrate low, and from this time on glycosuria was continuous and acidosis increased. The child was weak, lost weight, and did not grow in height. Acidosis became alarming about the middle of December, 1921, and after several attacks of threatened coma the patient was brought to the Institute as a last resort.

At admission she was conscious but excessively dyspneic, gasping for breath so rapidly and violently that speaking or swallowing was almost impossible. The plasma sugar was 0.833 per cent., the CO_2 capacity 27.1 vol. per cent., and very heavy lipemia was present. The child was remarkably obedient and cooperative, and during six hours took and retained about three liters of fluids, including 200 cc. of orange juice. At the end of this time all the chemical findings were slightly worse and the clinical condition began to appear hopeless. Consciousness had failed to a point where swallowing had become difficult, and the pulse at the wrist had become faint. Every effort had been made to treat the case without alkali, and the use of sodium bicarbonate was begun at a stage that seemed too late. The first 5-gram dose was followed by striking improvement within half an hour; the mother, who did not know what was given, commented on the wonderful effect of the medicine. A total of

TABLE 5

Case No. 918

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Jan.								
12	0	0	30	120	++++	833	...	....
13	0	0	100	400	++++	..	...	....
14	0	0	50	200	++++	...	...	....
15	2	0	25	108	++++	652	...	....
16	2	0	12	56	++++	..	...	....
17	3	0	5	32	++++	.	...	....
18-19	5	0	5	40	+	...	...	....
20-21	10	0	0	40	0	171	...	....
22-31	15	0	0	60	0	169	28	....
Feb.								
1-3	15	0	0	60	0	174	25	....
4-6	15	0	0	60	0	139	25	....
7-9	15	5	3	117	0	125	25	....
10-11	20	4	5	136	0	...	25	....
12	15	6	3	116	0	...	...	....
13-15	20	5	5	145	0	138	24	....
16-18	20	10	5	190	0	135	24	....
19-22	15	25	3	300	0	098	24	....
23-26	20	27	5	350	0	175	23	....
27	1	0	5	24	0	...	24	....
28	20	27	5	350	+	206	...	....
Mar.								
1-2	20	27	5	350	+	..	24	....
3-6	15	18	5	250	0	...	25	....
7	0	0	5	20	+	275	24	....
8	15	18	5	250	+	...	...	....
9	5	4	0	56	0	275	24	....
10	9	0	0	36	0	115	26	....
11-13	20	22	5	300	0	200	25	....
14	5	0	5	40	0	...	...	....
15-18	20	4	5	200	0	112	26	....
19-23	20	11	5	200	0	107	26	....
24-26	22	19	8	275	0	...	26	....
27	10	2	0	58	0	...	25	....
28-30	22	17	8	275	+	...	25	....
31	20	11	5	200	+	285	...	....
April								
1	20	11	5	200	0	...	...	....
2	15	18	5	250	0	106	25	....
3-5	20	15	5	250	0	...	24	....
6	10	2	0	58	0	91	...	....
7-12	20	16	5	250	0	195	25	....
13	10	3	0	67	0	...	...	....
14-20	20	16	5	250	0	130	25	....
21	10	3	0	67	0	...	24	....
22-24	20	16	5	250	0	184	24	....
25	10	15	3	187	++	416	25	....
26-27	10	1	0	49	0	138	25	....
28-30	10	9	1	125	0	142	24	....
May								
1-3	10	9	1	125	0	124	24	....
4-6	15	13	5	200	0	209	24	....

TABLE 5.—*Continued*

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
May								
10-14	15	12	1	175	0	150	23	
15-20	20	9	1	175	0	182	23	
21	20	10	1	175	0	126	23	
22	10	4	0	76	0	...	...	
23-31	20	10	1	175	0	143	23	
June								
1-6	20	10	1	175	0	192	24	
7-9	10	6	1	100	0	133	23	
10-14	10	6	1	100	0	173	23	
15-16	10	6	1	100	0	120	23	
17-20	10	6	1	100	0	156	23	
21-24	10	6	1	100	0	199	23	
25	10	2	0	58	0	111	23	
26-30	15	3	0	87	0	121	23	
July								
1	15	4	0	96	0	...	23	
2-6	10	4	0	80	0	146	24	
7-15	10	4	0	80	0	150	24	
16-20	10	4	0	80	0	135	23	
21-23	10	7	0	100	0	..	23	
24-31	10	6	0	100	0	128	23	
Aug.								
1-2	10	6	0	100	0	92	23	
3-5	10	8	1	120	0	...	22	
6-8	12	18	1	220	0	118	...	
8	12	18	1	220	0	138	22	
9-10	15	25	2	300	+	300	...	⅓
11-12	15	25	2	300	++	366	23	½
13-14	25	31	5	400	0	59	23	4
15-16	30	37	10	500	0	59	23	3
17	60	60	6	804	0	127	23	3
18-19	60	60	6	804	0	58	22	2
20-21	60	60	20	860	0	160	23	2
22-24	60	60	20	860	+	312	22	2
25-28	60	60	20	860	0	242	22	3
29-31	60	60	20	860	+	238	22	3
Sept.								
1	60	60	20	860	0	272	22	....
2	60	60	20	860	0	319	...	3
3-5	60	60	20	860	+	250	23	3
6-11	60	10	5	350	+++	...	22	3
12-16	60	10	5	350	++	349	22	3
17-19	60	10	5	350	++	441	21	3
20-23	60	10	5	350	++++	375	22	3
24-26	60	10	5	350	0	350	22	3
27-31	60	10	5	350	0	...	21	3
Oct.								
1-5	60	10	5	350	++	416	21	5
6-9	60	10	5	350	0	214	..	5
10-12	60	10	5	350	+	364	21	5
13-14	60	10	5	350	0	484	21	5
15-19	60	10	5	350	++	441	21	6
20-26	60	10	5	350	+	242	21	6
27-29	60	10	5	350	0	142	21	8

TABLE 5.—*Continued*

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Oct. 30-31	60	22	15	500	0	...	...	12
Nov. 1	60	46	9	691	0	91	21	12
2-6	60	60	6	804	0	145	22	12
7-12	60	97	20	1200	0	187	24	12
13-18	60	97	20	1200	0	148	24	12
19-23	60	97	40	1280	+	270	25	12
24-26	60	97	55	1340	0	68	25	12
27-30	60	97	55	1340	0	254	26	8
Dec. 1-2	60	97	55	1340	0	187	27	8
3-6	60	122	40	1500	0	357	28	8
7-10	60	122	40	1500	0	306	28	12
11-15	60	122	40	1500	+++	306	...	12
16-20	60	91	60	1300	+	250	29	12
21	60	91	60	1300	0	...	...	12
22	Discharged At home							
23-31 1923	60	91.1	60	1300	+++	...	29½	12
Jan. 1-7	50	75.5	30	1000	+	...	31½	12
8-16	50	75.5	30	1000	0	...	31½	16
31	Readmitted 55	101	30	1250	0	270	32	16
Feb. 1-6	55	101	30	1250	++	341	32	12
7-12	55	101	30	1250	++	220	32	12
13-19	55	101	30	1250	+++	375	32	16
20	55	101	30	1250	0	250	32½	16

25 gm. was given by the following morning and all acidosis symptoms cleared up. This is one of the experiences that have caused us to continue to use alkali as part of the treatment for coma.

On Jan. 13, 100 gm. of carbohydrate in fruit juices was the only food given. This quantity was reduced and vegetables substituted, until by Jan. 19 the urine was free from sugar and acetone. The attempt to build up a diet seemed at first to proceed as usual, until it was found in February and March that the tolerance was scarcely more than 200 calories, as judged not only by hyperglycemia but by actual glycosuria. Active diabetes in a case of this severity would mean probably one of two things; either rapid emaciation on a fat-poor diet or early coma on a fat-rich diet. The situation was explained to the parents, and they chose to continue the undernutrition in the hope of building up a tolerance sufficient to maintain life on any basis whatever. The ensuing record represents failure in this attempt. If there were many such cases, the entire under-

nutrition treatment would be a failure, but persons experienced in this treatment will understand the rarity of cases of the hopeless degree of severity here represented. The loss of weight was largely masked by water retention, though visible edema was prevented by regulation of the salt intake. The child became very weak and listless, but was never bed-ridden. The record proves the low level to which metabolism must be reduced, in order for a young child to withstand such a program for seven months. The maintenance of strength by small allowances of protein is also illustrated, showing that the abandonment of undernutrition after a few days of complete fasting, according to the custom of some practitioners, is entirely unnecessary if this method is given a trial.

This patient was chosen among the first group to receive insulin. In preparation, the diet was gradually increased, beginning Aug. 6, from 10 gm. protein and 120 calories, on which the plasma sugar had been normal, to 15 gm. protein, 2 gm. carbohydrate and 300 calories, which promptly gave rise to hyperglycemia and glycosuria, Aug. 9 to 12.

Insulin treatment was begun with 1/3 unit on August 10, which temporarily lowered the blood sugar, as shown in table 26, but neither this nor ½ unit on August 11 prevented a rise to 0.366 per cent. on the morning of August 12. Larger doses of 4 or 3 units not only prevented hyperglycemia but also resulted in slight hypoglycemic symptoms. With dosage of 2 units (½ unit every six hours) on August 18 and 19 the plasma sugar rose to 0.160 per cent. by the morning of August 20.

The diet meantime was gradually increased as shown in Table 5. From August 20 to Sept. 5 it consisted of 60 gm. protein, 20 gm. carbohydrate and 860 calories. Three units of insulin daily failed to compensate for this diet, and after increasing hyperglycemia, glycosuria began Sept. 5. With reduction of diet to 60 gm. protein, 5 gm. carbohydrate and 350 calories, this gradually cleared up. Hyperglycemia was only controlled by increasing the dosage as high as 8 units on October 27. A marked difference is thus shown between the conditions represented by absence of glycosuria on the one hand and by absence of hyperglycemia on the other. In our guidance of diet treatments, we have always believed that the mere absence of glycosuria is not a sufficient indication that the body is adequately supplied with pancreatic hormone, or in other words, that the strain upon the pancreatic function is relieved.

The further shifts of diet are shown in Table 5. Twelve units of insulin more than sufficed to provide for a diet as high as 60 gm. protein, 55 gm. carbohydrate and 1340 calories up to Nov. 26, so that the dosage had to be reduced to 8 units in order to prevent collapse symptoms. Beginning Dec. 3, carbohydrate was reduced and calories increased, making a diet of 60 gm. protein, 40 gm. carbohydrate and 1500 calories. Hyperglycemia promptly appeared, followed by glycosuria, which was not controlled by an increase of insulin dosage to 12 units. Beginning Dec. 16, an opposite change was made, making the diet 60 gm. protein, 60 gm. carbohydrate and 1300 calories. Glycosuria gradually cleared up, and the patient was discharged sugar-free on this regime on Dec. 22.

The influence of the increasing weight then made itself manifest. Gly-

cosuria returned at home, and the patient was readmitted Jan. 1. At her higher weight of 31½ lb., she was unable with 12 units of insulin to tolerate a reduced diet of 50 gm. protein, 30 gm. carbohydrate and 1000 calories, but this tolerance was gained by an increase of dosage to 16 units. After discharge on Jan. 16, she remained sugar-free at home until hypoglycemic symptoms, in the form of weakness and perspiration, began to appear evenings toward the close of January. The parents knew how to use carbohydrate to prevent danger, but brought the child back on Jan. 31 for further adjustment of diet.

An increase was given chiefly in the form of fat, making the diet 55 gm. protein, 30 gm. carbohydrate and 1250 calories. The dosage of 12 units proved insufficient, but on February 20 the patient was discharged sugar-free on this diet with 16 units of insulin.

Since her return home, the carbohydrate of this diet was increased to 50 gm., keeping the calories and the insulin the same. The condition did not run as smoothly at home, and various shifts of diet and dosage have been necessary in order to prevent either glycosuria or hyperglycemia. The diet has finally been reduced to 900 calories by reduction of fat, keeping the protein and carbohydrate unchanged. The insulin requirement thus runs between 9 and 12 units per day. With the high level of nutrition in such an extremely severe case, no distribution of meals or doses has seemed able to keep the patient free from one or the other form of symptoms. With the lower nutrition and lower dosage, it is believed that a smooth and uniform control will soon be attained.

This statement of technical difficulties has conveyed no idea of the transformed condition of the child. The extreme undernutrition prior to August 9 had demonstrated hopeless severity of diabetes. Extreme emaciation and weakness had been produced without creating a tolerance for any diet sufficient to maintain life. The child was too weak to climb stairs, and dreaded the exertion of walking even a few steps. Early death from either diabetes or starvation was inevitable. The transformation under insulin is shown by the accompanying pictures. The child has all she desires to eat, the nutritive state has been restored so that she weighs slightly more than before her diabetes, she has grown 2 inches, and her parents state that she was never stronger or more active and playful in her life. The purpose will be to keep her strong and adequately nourished but not fat.

Case No. 989. (Severe juvenile diabetes. Greatly improved nutrition with large insulin dosage. Tolerance test. Insulin requirement for fat.) Female. American. Age 8 years. Height 4 feet. Weight 47 lb. maximum, 42 lb. when seen in consultation Dec. 22, 1921. The family and personal history were unimportant. The girl was considered the strongest in a family of four children, and had had only trivial infections.

Consultation was called immediately upon the discovery of glycosuria by a pediatritian, which resulted from the mother's observation that the child's weight had fallen to 42 lb. within a few weeks while she was eating ravenously. She still had the appearance of perfect health, and the case at first appeared to be of recent acute onset, but closer inquiry re-

vealed that marked thirst and polyuria had been present for as long as a year. A specially trained nurse was placed in charge in the patient's home, and the diet was limited to 25 gm. protein, 25 gm. carbohydrate and 225 calories. As the glycosuria persisted, a change was made on December 25 to 20 gm. protein, 15 gm. carbohydrate and 225 calories. Glycosuria ceased during the next day, but the plasma sugar on December 31 was still 0.283 per cent. The disturbing feature then developed that these and lower diets, continued week after week, with one day of complete fasting each week, failed to reduce the plasma sugar below 0.15 or 0.16 per cent., and the slightest attempt at an increase gave rise immediately to marked hyperglycemia or actual glycosuria. Finally, on the chance that there might be some source of forbidden food which escaped the vigilance of the nurse, the patient was transferred to the Institute on February 12, 1922. The low tolerance was confirmed, but a diet limited strictly to 15 gm. protein resulted in a normal plasma sugar of 0.103 per cent. on February 20. The weight was reduced to a minimum of 32 lb. The patient had been kept free from serious hunger and was by no means bedfast, but the weakness and emaciation offered such an unpleasant contrast to the healthy appearance and actions at the time of beginning treatment that a very serious question was raised whether the treatment should be continued or the child fed so as to permit glycosuria. After several consultations and uniform agreement on the fatal prognosis with glycosuria, the treatment was continued in the attempt to save life even at the price of invalidism. The diet was gradually built up while keeping the plasma sugar normal, until the patient was discharged June 22, 1922, weighing 35 lb. on a diet of 40 gm. protein, 5 gm. carbohydrate and 800 calories. Though thin, she was able to be occupied all day long with games, walks, trips to moving picture shows and other light amusements.

With continuance of careful treatment at home, the tolerance, as judged by normal plasma sugars, rose to a maximum of 50 gm. protein, 15 gm. carbohydrate and 1000 calories. The patient returned to the Institute August 19 for the sake of insulin treatment.

Some of the subsequent details are given in paper No. 3 (Tables 7 and 23). Approximately 7 units of insulin was required to raise the diet to 60 gm. protein, 30 gm. carbohydrate and 1400 calories. Observations were made with a view to determining the tendency toward gain or loss of tolerance under insulin treatment.

Oct. 27, 1922, the patient had for three weeks been taking 18 units of insulin daily in order to assimilate a diet of 60 gm. protein, 30 gm. carbohydrate and 1200 calories, without glycosuria but with continuous moderate hyperglycemia. This seemed scarcely larger than the diet which she might have tolerated just prior to insulin treatment, had hyperglycemia been permitted then. In order to judge her assimilative capacity after 2 months of insulin treatment, all insulin was omitted for 5 days. Glycosuria began within 48 hours and steadily increased to 13.4 gm. on the final day, then ceased on the first day when 18 units of insulin was resumed. The weight at this time was 37 pounds. Likewise, on Dec. 14, 1922, the patient had been showing intermittent but increasing glycosuria for 2

weeks while taking 20 units of insulin and a diet of 60 gm. protein, 30 to 60 gm. carbohydrate and 1800 calories. Insulin was discontinued, and a single fast-day on Dec. 15 cleared the urine. A diet of 40 gm. protein, 10 gm. carbohydrate and 500 calories was then tolerated with normal plasma sugar, but an increase to 50 gm. protein, 10 gm. carbohydrate and 800 calories raised the plasma sugar to 0.192 per cent. within 3 days. The weight at this time was 42 pounds. The apparent fall of tolerance is fully explainable by the gain in weight. It is entirely natural that the tolerance at a weight of 37 pounds should be a trifle lower than at 35 pounds, and that it should be still lower at 42 pounds. The test showed, however, that the tolerance was distinctly higher than it had been at the identical weight of 42 pounds when the patient was first seen. It is uncertain to what extent this rise of tolerance may be attributed to the 8 months of low diet treatment and to what extent to the succeeding 4 months of insulin treatment. It was evident, however, that exactly 1 year after the time when the patient was first seen she had not lost but had gained slightly in assimilative power.

The experiments with exercise are discussed under table 7 in paper 3. The lowering of sugar by muscular work, familiar under diet treatment, seemed to be indicated also in these tests under insulin treatment.

The diet has slowly been increased to a maximum of 80 gm. protein, 150 gm. carbohydrate and 2000 calories, the assimilation of which without glycosuria has been found to require 70 units of insulin. This is the largest regular dosage yet given to any of our patients. It is distributed in four equal injections, six hours apart. The height has increased to 4 feet 1 inch, and the weight to 61 pounds, so that the child is slightly obese. In appearance she is healthy and beautiful, and in strength she is fully normal and capable of the hardest exertions and of normal spontaneous play.

Case No. 1016. (Very severe juvenile diabetes. Transformation with insulin.) Male. Hebrew. Age 16 years. Height 5 feet 1 inch. Weight 90 lb. maximum, 80 lb. at admission, November 1, 1921. Family history—Mother and one sister are obese. Another sister died of diabetes. A niece of the father has diabetes. The boy is said to have had no illness except measles when very young. Diabetes began with polyphagia and polydipsia three years ago. Lax diets were used to keep glycosuria absent most of the time, until during the past six months it has been continuous and uncontrollable.

At admission, glycosuria was heavy but ketonuria absent. The severity of the case is indicated by the fact that on a diet of only 20 gm. protein and 5 to 8 gm. fat daily, the urine on Nov. 25 still contained traces of sugar and the plasma sugar was 0.377 per cent. A more rigorous program was then begun, consisting of days of only 10 gm. of protein alternating with days of complete fasting. The urine thus became clear on Nov. 28, but the plasma sugar was 0.365 per cent. Under a similar program with fewer fast days, the plasma sugar was 0.319 per cent. on Dec. 9, 0.209 per cent. on Dec. 22, and finally 0.123 per cent. on Jan. 6. This extremely severe treatment reduced the body weight to 63 lb. The patient, though

weak, was by no means bedfast, but could go for rides or short walks and otherwise amuse himself all day long. The plasma sugar then remained normal while the diet was increased slightly to 20 gm. protein, 2 gm. carbohydrate and 400 calories. The patient was discharged on this diet Jan. 18, 1922, weighing 67 lb.

Under careful treatment at home, it became possible to increase the diet first to 600 calories and finally to 45 gm. protein, 10 gm. carbohydrate and 800 calories. Occasional tendencies to hyperglycemia were checked by temporary reductions of diet. On this basis, the patient lived the life of a weak and emaciated invalid, but it is to be noted, first, that life could not have been preserved in any other way with diabetes of such extreme severity, and second, that under these conditions there was no loss but a definite gain of tolerance. The patient was readmitted for insulin treatment Feb. 20, 1923, weighing 69 lb.

A diet of 60 gm. protein, 20 gm. carbohydrate and 1100 calories caused slight glycosuria within 24 hours, indicating the very close limitation of tolerance. Confirmation is furnished by the fact that dosage of 10 units of insulin stopped the glycosuria immediately but did not restore the normal level of the blood sugar within four days. After increases of diet and dosage, the patient was discharged March 20, 1923, on 80 gm. protein, 70 gm. carbohydrate, 1820 calories, and 15 units of insulin per day, at a weight of 75 lb. This dosage was not fully adequate to prevent glycosuria, and increases have since been made to 2200 calories and to 24 units of insulin. The weight has risen to 85 pounds. The transformation accomplished by insulin in a case of this severity requires no comment.

Case No. 1020. (Moderate juvenile diabetes. Measurement in insulin dosage of the loss of tolerance from violations of diet, also the difference between hyperglycemia and normal blood sugar.) Female. Irish-American. Age 10 years. Height 4 feet 7 inches. Weight 75 lb. maximum, 58 lb. at admission, Nov. 5, 1921. Family history negative. The patient had measles, whooping cough and scarlet fever in her early years, and frequent tonsillitis up to tonsillectomy one year ago. Loss of weight began in August, 1921, and she was treated with tonics by the family physician until the diagnosis of diabetes by a physician on the day before admission to the Institute. After undernutrition to check glycosuria and acetonuria, it became possible to build up the diet to 60 gm. protein, 25 gm. carbohydrate and 1400 calories. After discharge on Dec. 1, 1921, the child felt well, attended school, and remained free from hyperglycemia until she began to break diet in November, 1922. Notwithstanding repeated reductions of diet by the parents, the thefts of food and outbreaks of glycosuria continued. She was returned to the Institute for insulin treatment Jan. 10, 1923, with heavy glycosuria but no ketonuria. The height was 4 feet 8½ inches, and the weight 58 lb. Strict undernutrition arrested the glycosuria by Jan. 16, and after a slight increase of diet, insulin treatment was begun Feb. 2. Slight hyperglycemia of 0.168 per cent. developed with 4 units of insulin daily as the diet was increased to 35 gm. protein, 5 gm. carbohydrate and 900 calories, but normal plasma sugar was then maintained by an increase to 6 units daily. Here the dif-

ference between high and normal plasma sugar seemed to be 2 units of insulin. During the following three weeks the diet was increased to the former level of 60 gm. protein, 25 gm. carbohydrate and 1400 calories, in order to learn what insulin dosage was now necessary for the assimilation.

It is noticeable that no tolerance was lost on careful diet in the eleven months from Dec. 1, 1921, to Nov. 1, 1922, as judged by the maintenance of constant weight and normal blood sugar. The progressive possibilities of the case are indicated by the loss of tolerance occurring with violations of diet and frequent glycosuria in the three months from the 1st of November, 1922, to the beginning of February, 1923, which could be estimated in terms of insulin by the fact that a dosage of 10 units per day was found necessary to abolish glycosuria on the former diet at the same body weight. Clinically, the most important feature is that the loss of tolerance which would formerly have been irreparable can now be compensated by the use of insulin. At home the diet has been raised to 60 gm. protein, 50 gm. carbohydrate and 1700 calories. The weight has not risen about 60 pounds, though the strength is entirely satisfactory. As the same dosage of 10 units of insulin still suffices on the higher diet, it seems probable that there has been some real recovery of tolerance.

Case No. 1029. (Moderate diabetes. Improvement with insulin.) Female. American. Age 41 years. Height 5 feet 2 inches. Weight 182 lb. maximum, 126 lb. at admission, Nov. 11, 1921. Family history negative except for hypertension and apoplexy. Personal history negative except for hypertension for some years past. The entire loss of weight is said to have occurred since March, 1921. Polyuria began in July, but the urine was reported negative for sugar. Glycosuria was first discovered one week before admission. The case proved unexpectedly severe, and a diet of approximately 30 gm. protein per day for three weeks was necessary to bring the plasma sugar to normal. The patient was discharged Dec. 21, 1921, on 60 gm. protein, 10 gm. carbohydrate and 800 calories, at a body weight of 117 lb. With further improvement at home, it became possible to increase this diet to 65 gm. protein, 15 gm. carbohydrate and 1600 calories. The condition remained favorable until recently the patient exceeded the quantitative limits. She was therefore readmitted Feb. 13, 1923, with slight glycosuria and weighing 109 lb.

Up to Feb. 17, she proved unable to tolerate a diet of 55 gm. protein, 10 gm. carbohydrate and 1300 calories. Insulin treatment was therefore begun, and she was discharged March 6, 1923, on 80 gm. protein, 50 gm. carbohydrate, 2400 calories, and 10 units of insulin divided in two injections per day. The weight was 115 lb., and there was appreciable gain in strength. Hyperglycemia was present, and it has since been necessary to increase the insulin to 18 units daily in order to prevent glycosuria.

Case No. 1034. (Juvenile diabetes, uncontrollable by diet. Continuous institutional observation for 1 1/3 years. Greatly improved with insulin on identical diet. Insulin requirement for fat. Rise of tolerance.) Male. American. Age 8 years. Height 4 feet. Weight 50 lb. maximum, 43 lb. at admission, Nov. 19, 1921.

The family history was negative for hereditary disorders. The patient had had measles, mumps, chickenpox and whooping cough before the age of 5. He also suffered frequently from tonsillitis, though the tonsils were not removed until after the onset of diabetes. Otherwise he was a strong, healthy, perfectly normal boy. After two or three weeks of thirst and polyuria, diabetes was diagnosed Dec. 15, 1919. A low carbohydrate diet, unrestricted in protein and fat, failed to control the condition. After six weeks, a change was made to another physician, who stopped the glycosuria by three days of undernutrition. After three months of sugar freedom, however, the tolerance permitted only a diet of 30 gm. protein, 20 gm. carbohydrate and 45 gm. fat, with one day of 10 gm. protein, 10 gm. carbohydrate and 10 gm. fat. Any attempts to increase the diet caused glycosuria. He withstood tonsillectomy uneventfully in April, 1920. He remained free from glycosuria on the diet mentioned until August, 1920. Owing to minor errors of diet at home, glycosuria then returned and was present continuously. Owing to weakness, boils, and the usual distressing symptoms, an attempt was made to clear up the sugar by eight days of fasting in September, 1921, without result. Later, persistent symptoms of severe acidosis necessitated omitting most of the fat from the diet, and emaciation and weakness then progressed more rapidly.

On admission to the Institute, the weight was 33 lb. and glycosuria and acetonuria were heavy, but there were no clinical symptoms of acidosis. There was nothing to distinguish the case from the numerous ones which come with the history of being impossible to make sugar-free by fasting, until the failure of the strict undernutrition from November 19 to 28 to alter appreciably either the urine or the blood sugars suggested that the statement might be correct in this instance. (cf. paper 3, table 11.) The analyses then undertaken showed that the D:N ratios were almost "total." The program of almost complete starvation was continued for nearly a month, namely to Dec. 15. It was then attempted with a diet of 50 gm. protein to preserve the strength while continuing undernutrition, but by January 1 it seemed sufficiently evident that the D:N ratios could not be reduced. The diet was then raised to 650 calories by addition of fat, and arrangements were made for studies of the respiratory metabolism by Drs. Du Bois and Richardson in the Russell Sage Institute of Pathology in New York, where the patient was transferred on Jan. 5.

This study showed that the diabetes was not quite "total," and the D:N ratios obtained there were sometimes as high as 3.9 but sometimes as low as 1.2, generally in the neighborhood of 3.0. The higher ratios obtained by us must therefore be regarded as due to the "fillers" used in the diet. Apart from mineral oil and agar, these consisted of 8 bran biscuits and 600 gm. of thrice-cooked vegetables daily. In addition, the rather liberal use of sugar-free flavoring extract may require consideration. A test of the bran biscuits was made by giving 18 of them on Jan. 4, representing 174 gm. of dry bran. It will be noticed that the D:N ratio for this day did not rise appreciably, and the quality of the bran biscuits seems to be assured by this test.

On the patient's return on Feb. 6, 1922, he was kept on the same diet on

which he had been placed in the Russell Sage Institute, namely, 60 gm. protein, 60 gm. fat, and 6 gm. carbohydrate, making 804 calories. Though weak, the boy was always courageous and cheerful, by no means bedfast, and usually up and about all day. He was slightly stronger on the diet mentioned than at the close of the undernutrition program on Jan. 1. Marked acidosis is indicated by the high figures for urinary ammonia. Clinical symptoms remained absent nevertheless, without alkali administration. A strong tendency to edema had to be held in check by a strict salt-free diet, such as used for certain nephritis and hypertension cases, but nevertheless water retention largely masked the loss of body substance. For incidental reasons analyses of sugar and nitrogen were omitted during the first week after the patient's return. The subsequent record is monotonously uniform, therefore only sample portions are given in table 11 of paper 3. The daily record is resumed from June 25 onward, introductory to the use of insulin. Chemically, it will be observed that the condition changed little. Clinically, the diet served to keep the boy from fatal acidosis while allowing him slowly to starve to death. In the early part of August it was evident that the end was not far distant. Signs of acidosis were increasing, while emaciation and weakness had reached a point such that the patient was able to be up only for short periods each day.

The use of insulin was begun on August 10. The immediate effects of the first small doses upon the blood sugar are shown elsewhere in this paper (table 26). The giving of 8 units, in four doses of 2 units each, abolished glycosuria and acetonuria on August 13. On August 15 the plasma sugar remained below 0.1 per cent., and the doses were therefore decreased. It was striking that glycosuria could be kept absent in this hopelessly severe case by as little as 4 units per day. A trace of sugar returned promptly with the reduction of the dose to 2 units on August 30, and increased rapidly when a psychic effect was excluded by the giving of 4 injections of salt solution on August 31. It ceased with the resumption of 4 units of insulin on Sept. 1 and 2.

The strength was greatly improved, and the weight was beginning to show an increase due to better utilization of the identical diet. Accordingly, the dose of 4 units began to prove inadequate. Hyperglycemia and traces of glycosuria were present from Sept. 3 onward, and, after 6 units had proved inadequate on Sept. 8 and 9, the urine was cleared only by 8 units following Sept. 10. Hyperglycemia still continued on this dose, which had produced hypoglycemia when the patient weighed two or three pounds less.

Experiments with modifications of the diet were then performed as described in paper 3 (table 11). Also, the patient was sent to the Russell Sage Institute on Nov. 15 for studies of his respiratory metabolism under the new conditions, and returned on Dec. 26. The subsequent portions of the record show the lower nitrogen excretion and positive nitrogen balance under the influence of insulin. The weight had risen to approximately 38 lb., and 8 units of insulin no longer sufficed for control, as shown by the continuous hyperglycemia and frequent glycosuria. The

variations are due to the use of this patient at this time for testing the potency of different lots of insulin. In particular, the absence of glycosuria and reduction of hyperglycemia following Jan. 28 were due to insulin which proved unusually strong and which caused hypoglycemic reactions in certain other patients. The increase of carbohydrate to 26 gm., from Jan. 18 onward, with reduction of fat so as to keep the total calories unchanged at 804, proved to be a minor factor without any perceptible influence upon the condition.

February 9 to 27, insulin was omitted in order to observe any possible changes from exactly six months of insulin administration. Glycosuria returned immediately upon the reduction of the dose on Feb. 8, and was continuous thereafter. It was, however, much less than in the period before insulin treatment, and the carbohydrate balance remained decidedly positive. Absolute fasting was then employed for four days, Feb. 21 to 24, to ascertain whether glycosuria could now be stopped by this means. The sugar excretion fell to amounts too low to titrate on Feb. 22, 23 and 24, but these traces increased on the 24th as compared with the 23rd, and the plasma sugar also rose. It was considered inadvisable under these circumstances to prolong the fast further.

With resumption of the former diet the former glycosuria returned, and was promptly abolished by the use of 8 units of insulin from Feb. 28 onward. In order to test the possibility of a still higher tolerance with this 8 unit dosage, the diet from March 4 to March 9 was increased to 60 gm. protein, 60 gm. carbohydrate, and 1500 calories. The resulting glycosuria was not controlled by an increase of insulin to 12 units on March 8, or to 16 units on March 11, though the fat meanwhile had been reduced on March 10 so as to make only 1200 total calories. Further experimental details are given in paper No. 3.

The influence of the prolonged insulin dosage upon the patient's own pancreatic function may be judged by two standards. On the one hand, the diminished glycosuria, positive carbohydrate balance, and greater tendency to cessation of glycosuria with fasting would seem to indicate a genuine gain in tolerance. Such improvement might easily be explained on the assumption that the pancreatic islands, with the unusually complete functional rest afforded by insulin treatment, were capable of some degree of repair or hypertrophy. On the other hand, the requirement for insulin dosage has not diminished. At the lowest level of body weight, 4 units sufficed and 8 units proved excessive. With a gain of two or three pounds of weight, 8 units was the proper dose. With a further gain of two or three pounds, 8 units abolished glycosuria only when the insulin was particularly strong, and a higher diet required a great increase of dosage. The later evidence (paper 3) seems to demonstrate a distinct gain in tolerance.

One of the most interesting features of this case is that all the earlier changes, chemical and clinical, were obtained essentially on the same diet of 804 calories. The condition of the boy was completely transformed. He has gained weight and particularly strength, and is active from morning till night. The changes shown in his pictures took place on the identical diet, because at first this diet could not be assimilated and later it was

normally assimilated under the influence of insulin. The weight and strength are not yet equal to normal, and there has been no gain in height. The condition can now be further improved by higher diets and higher insulin dosage.

Case No. 1044. (Severe diabetes. Insulin requirement for fat. Improved nutrition. Doubtful prognosis because of carelessness.) Male. American. Age 47 years. Height 5 feet 11 inches. Weight 168 lb. maximum, 135 lb. when first seen and placed on a diet Nov. 30, 1921. Admitted to the Institute Dec. 31, 1921. Diabetes in a maternal aunt is the only instance of hereditary disorder in the family. The personal history was negative except for typhoid at 8 years of age. There has been no obesity in the patient or his family. In military service, he had influenza in January, 1918, and the acute onset of typical diabetic symptoms led to the discovery of glycosuria in February. Dietary restrictions kept glycosuria absent most of the time for two and a half years, but the patient has often been careless and especially has gone to extremes in occasional fits of depression. For six months before coming to the Institute he paid little attention to diet and had continuous and increasing glycosuria and acidosis. His weight when first seen was 135 lb. Rigorous and prolonged undernutrition was necessary to control glycosuria and hyperglycemia, and he was discharged March 5, 1922, with a weight of 126 lb. (due partly to invisible water retention) on a diet of 55 gm. protein, 15 gm. carbohydrate and 1300 calories. His outlook was only one of invalidism.

He was again careless with diet, and was readmitted May 11, 1922, with sugar but not acetone present, and discharged without glycosuria but with hyperglycemia on May 18. Though faithful to treatment in the Institute, he again quickly broke diet outside, and was readmitted on June 21 with glycosuria and acetonuria both heavy. A diet limited to 20 gm. protein and 5 gm. carbohydrate cleared the urine by July 8, but the plasma sugar had fallen only from 0.536 to 0.334 per cent. The addition of 33 gm. of fat, so as to raise the total calories to 400, increased the plasma sugar to 0.375 per cent. and therefore had to be discontinued. The diet was then limited first to 40 and then to 30 gm. of protein daily, but by August 8 this severe program had reduced the plasma sugar only to 0.255 per cent. A diet of 35 gm. protein, 23 gm. fat and 350 calories was begun on August 9, and by the following morning the plasma sugar had risen slightly to 0.270 per cent. Water retention, with slight visible edema, had raised the body weight to 134 lb. notwithstanding salt-free diet. It became evident that tolerance for a living diet could not be acquired.

Insulin treatment was therefore begun on August 10. The first small doses of 1/3 and 1/2 unit had slight but perceptible effects upon the plasma sugar (table 27). The injection of 5 cc. of salt solution on August 12 produced a strong psychic effect, because the patient supposed that he was receiving a greatly increased dose of insulin, but the influence upon the plasma sugar was lacking. After omission of injections on August 13 and 14, doses of 3 units on August 15 and 16 reduced the plasma sugar nearly to normal.

The subsequent treatment, beginning with 1 unit of insulin daily, is shown in paper No. 3 (table 1). The diet was gradually increased to 50 gm. protein, 10 gm. carbohydrate and 1600 calories, and the insulin to 6 units daily. The patient was discharged on this program October 23, 1922, without glycosuria and with only slight hyperglycemia. The weight was 131 lb. without edema, and the strength and spirits were greatly improved. It was understood that this incomplete result should suffice for the time being and that the patient would return later when the supply of insulin had become more abundant.

It is known that the patient has received increased insulin dosage elsewhere, and has continued his indiscretions in diet and has had heavy glycosuria. His clinical condition has nevertheless been greatly improved by insulin, at least temporarily.

Case No. 1054. (Very severe diabetes. Increase of insulin requirement by "basal" diet.) Female. American. Age 41 years. Height 5 feet 6 inches. Weight 150 lb. maximum four years ago, 105 lb. at admission, Feb. 5, 1922. Family history negative. Personal history—"bloody dysentery" at 14; operation for appendicitis 20 years ago; albuminuria and eclampsia at birth of her first child 14 years ago; influenza 8 years ago, followed in one week by jaundice. The first symptom of diabetes was thirst and polyuria in June, 1918, and the diagnosis was made four months later. The case has been very severe and only partially controllable by any diets used. The glycosuria and acetonuria present when the patient was first seen in consultation cleared up with two weeks of rigid semi-starvation at home, but the plasma sugar was still 0.428 per cent. when the patient was admitted to the Institute. The diet was first nothing but 25 gm. protein daily, later only 15 gm. protein with alternate fast days. The plasma sugar remained approximately 0.300 per cent., and attempts to increase the diet caused prompt glycosuria. The patient was discharged March 8, 1922, to continue the inanition program at home. She was very weak though not bedfast. Slight edema was responsible for the weight of 104 lb.

The inability to develop any tolerance was discouraging to all concerned, and no objection was made when the patient preferred to take an ordinary type of diabetic diet at home. Denutrition was not arrested by eating, and she was readmitted for insulin treatment Sept. 27, 1922, with glycosuria and ketonuria, at a weight of 83 lb. On a diet of nothing but 15 gm. protein, insulin was given beginning with 1 unit and increasing to 5 units per day. Glycosuria thus ceased by Oct. 8 and ketonuria fell to traces, but the plasma sugar was 0.405 per cent. Oct. 10, 0.445 per cent. Oct. 14, and 0.300 per cent. Oct. 22. Insulin was then increased to 8 units, and the diet to 20 gm. protein, 2 gm. carbohydrate and 300 calories, with the result that the plasma sugar fell to 0.175 per cent. by Nov. 3. During the following three weeks the diet and dosage were gradually increased, and with 50 gm. protein, 20 gm. carbohydrate, and 1000 calories, 16 units of insulin per day was inadequate, as shown by the rise of plasma sugar to 0.366 per cent. and the return of glycosuria. The patient was discharged Dec. 3, 1922, on a diet of 50 gm. protein, 10 gm. carbo-

TABLE 6

Case No. 1054

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Sept. 30	15	0	0	60	++++	469	...	1
Oct. 1	"	"	"	"	++++	...	83	1
2	"	"	"	"	++++	...	...	1
3	"	"	"	"	++++	405	86	1
4	"	"	"	"	++++	...	...	1
5	"	"	"	"	++++	...	88	2
6	"	"	"	"	++++	429	...	2
7	"	"	"	"	++++	...	88	5
8	"	"	"	"	0	...	...	5
9	"	"	"	"	0	...	87	5
10	"	"	"	"	0	405	...	5
11	"	"	"	"	++	...	88	5
12	"	"	"	"	++	...	...	5
13	"	"	"	"	++	...	88	5
14	"	"	"	"	++	445	...	5
15	"	"	"	"	+++	...	87	5
16	"	"	"	"	+++	441	...	5
17	"	"	"	"	++	...	88	5
18	15	15	0	200	+	...	...	0
19	"	"	"	"	+	395	87	2
20	"	"	"	"	+	...	...	5
21	"	"	"	"	0	...	...	5
22	"	"	"	"	0	300	...	5
23	"	"	"	"	0	...	87	8
24	"	"	"	"	0	...	...	8
25	"	"	"	"	0	...	85	8
26	"	"	"	"	0	250	...	8
27	"	"	"	"	0	...	86	8
28	"	"	"	"	0	...	...	8
29	20	23	2	300	0	...	86	8
30	"	"	"	"	0	...	...	8
31	"	"	"	"	0	184	88	8
Nov. 1	"	"	"	"	0	...	...	8
2	25	42	5	500	0	...	84	8
3	"	"	"	"	0	...	...	8
4	"	"	"	"	0	175	84	8
5	35	57	10	700	0	...	...	10
6	"	"	"	"	0	...	82	10
7	50	80	20	1000	0	234	...	16
8	"	"	"	"	0	250	84	16
9	"	"	"	"	0	...	...	16
10	"	"	"	"	0	...	85	16
11	"	"	"	"	0	272	...	16
12	"	"	"	"	0	...	85	16
13	"	"	"	"	+	326	...	16
14	"	"	"	"	+	...	82	16
15	"	"	"	"	0	349	...	16
16	"	"	"	"	++	...	84	16
17	"	"	"	"	++	...	...	16

TABLE 6.—*Continued*

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Nov.								
18	50	80	20	1000	++	366	...	16
19	"	"	"	"	+	...	...	16
20	"	"	"	"	+	...	85	16
21	"	"	"	"	++	...	...	16
22	"	"	"	"	++++	...	86	12
23	50	180	10	1860	+++	366	...	16
24	"	"	"	"	++++	...	85	16
25	"	"	"	"	++++	...	...	16
26	"	"	"	"	++	...	86	16
27	"	"	"	"	0	...	...	16
28	"	"	"	"	0	283	86	8
29	"	"	"	"	0	...	...	8
30	"	"	"	"	++	...	86	16
Dec.								
1	"	"	"	"	0	...	...	16
2	"	"	"	"	0	203	...	16
3	"	"	"	"	0	226	...	4

hydrate, and 1860 calories, for which the insulin dosage was not precisely determined. Her weight at discharge was 86 lb. and her strength considerably improved. She has since continued insulin treatment at another clinic.

It is doubtful if glycosuria could have been stopped by fasting at the second admission. As it ceased with the aid of only 5 units of insulin, it is probable that the patient's pancreas was still functioning to the extent of a few units of insulin per day. The difference between semi-starvation and a so-called "basal" diet is again illustrated numerically, inasmuch as a dosage of at least 16 units of insulin daily was required for the diet of 1000 calories.

Case No. 1065. (Severe juvenile diabetes. Influence of fat feeding on insulin requirement. Influence of mild infection.) Female. American. Age 15 years. Height 5 feet 4 inches. Weight 108 lb. maximum, 80 lb. at admission, January 4, 1922. Family and personal history negative. This case was described in previous publications,[8, 12] as specially difficult to control. Diabetes was diagnosed Feb. 1, 1920, three weeks after acute onset of hunger, thirst and weakness. A fast of five days stopped glycosuria, and after eight months she tolerated 125 gm. protein, 75 gm. carbohydrate and 2500 calories. Glycosuria then reappeared, treatment was abandoned in September, 1920, and the downward course has been continuous. There were several attacks of threatened coma, and intense glycosuria and acetonuria were present at admission. The stringent treatment required has been previously shown. Owing to the extremely

low ration, the negative nitrogen balance amounted to 195.4 grams in 82 days, though there was nothing resembling "azoturia." The diet at discharge, June 4, 1922, and subsequently at home approximated 35 gm. protein, 5 gm. carbohydrate, and 600 calories. Hyperglycemia was continuous on this diet, and glycosuria was kept absent only by the use of one day of almost complete fasting each week.

The patient was readmitted for insulin treatment Nov. 11, 1922. The detailed record is given in paper No. 3 (Table 9). She was discharged Jan. 25, 1923, with slight glycosuria present on 50 gm. protein, 40 gm. carbohydrate, 1500 calories, and 30 units of insulin, divided in three injections per day. Though the weight at discharge was the same as at admission, there had evidently been a considerable replacement of water by fat in the tissues. The estimate of the dosage at discharge proved correct, for the glycosuria quickly cleared up and has remained absent except at the onset of a mild attack of influenza on Feb. 22. An increase of the dosage by 3 units per day stopped the sugar immediately and within three days the former dosage could be resumed. The weight has risen to 82 lb., and the rising blood sugar indicates the probable need of an increase of dosage soon. The girl has returned far toward health and strength under insulin. Menstruation, which had ceased as usual in severe diabetes, has returned.

Case No. 1069. (Severe juvenile diabetes. Influence of total calories and body weight on insulin requirement.) Female. Jewish-American. Age 15 years. Height 4 feet 10 inches. Weight 72 lb. maximum, 62 lb. at admission, December 19, 1921. Family history negative except that a paternal uncle weighs 200 lb. Personal history negative. Evident symptoms of diabetes had been present at least since August, 1921, but the diagnosis was missed by the family physician and only made by a consultant three days before admission.

The heavy glycosuria and ketonuria cleared up on four days of a diet limited to 25 gm. protein and 5 gm. carbohydrate, but up to Jan. 13 the plasma sugar had fallen only to 0.162 per cent. on this diet. Undernutrition was then continued and a diet gradually built up, until the patient was discharged Feb. 22, 1922, with normal plasma sugar on 45 gm. protein, 10 gm. carbohydrate and 950 calories, at a weight of 57 lb.

Difficulties were encountered at home, and in September the patient spent a week in the Institute for clearing up glycosuria. The same difficulties returned, and she was readmitted Nov. 20, 1922, with a view to insulin treatment. The detailed record is given in paper No. 3 (Table 8). The patient was discharged Feb. 17, 1923, on a diet of 80 gm. protein, 50 gm. carbohydrate, and 2000 calories, with 15 units of insulin divided in three injections daily. The weight had risen from 58 lb. at this admission to 63 lb. at discharge, and the strength and spirits were much improved. At home, the increase of weight is continuing, and it has become necessary to increase insulin to 21 units in order to check the frequent returns of glycosuria.

Case No. 1073. (Severe diabetes. Insulin requirement for protein,

carbohydrate and fat. Great improvement in physical and psychic condition.) Male. American. Age 26 years. Height 5 feet 10 inches. Weight 148 lb. maximum, 112 lb. at admission, Dec. 28, 1921. The family and personal history were unimportant. The diabetes was of 5 years' standing. Glycosuria had been controlled by diet during the first three years but had been continuous in the two years preceding admission.

Heavy glycosuria and acidosis, without coma symptoms, were present at admission, and the weight of 106 lb. seemed to be due to extreme dryness of the body, and from subsequent observations a fair estimate of the true body weight seemed to be about 112 lb. The glycosuria proved extraordinarily stubborn. A program of days of 25 gm. protein (carbohydrate-free and nearly fat-free) alternating with days of complete fasting finally cleared the urine for the first time on Jan. 31. The plasma sugar was correspondingly difficult to influence, and from the level of 0.417 per cent. at admission it had fallen only to 0.348 per cent. by Jan. 31. During this period of more than a month of extreme undernutrition the strength was remarkably little diminished. The sustaining qualities of small amounts of protein during such a period have apparently not been generally appreciated. A regular diet of 15 gm. protein and 7 gm. fat reduced the plasma sugar to 0.153 per cent. on Feb. 10, and less severe undernutrition in the form of 35 gm. protein, 5 gm. carbohydrate and 700 calories brought it to a normal level of 0.107 per cent. on Feb. 16. The weight was then 108 lb. without visible edema, and the patient was still feeling well and was able to take walks of fair length. He was discharged April 25, 1922, weighing 112 lb., on a diet of 50 gm. protein, 10 gm. carbohydrate and 1100 calories, in good condition as a semi-invalid but unfit for work.

The patient was strictly faithful, but on finding his attempts to work unsuccessful he became despondent and intentionally abandoned all dietary restraint. His previous symptoms quickly returned and increased rapidly. His family learned of insulin, and only with extreme difficulty persuaded him to return to the Institute on July 22, in the hope of gaining tolerance for a diet sufficient to enable him to carry out his ambitions. The weight had fallen to 103 lb., and advanced weakness and acidosis symptoms were present. The plasma sugar was 0.385 per cent. and the plasma bicarbonate 46.6 vol. per cent. On a diet limited to 30 gm. protein and 7 to 20 gm. fat daily, acetonuria cleared up almost completely by August 10, but glycosuria still persisted. From the fact that the sugar excretion had fallen to traces on August 8 and had increased to titratable amounts on the following day, and that the plasma sugar had risen from 0.357 per cent. on August 8 to 0.405 per cent. on August 10, it was evident that sugar freedom could be obtained only by extreme inanition if at all.

It is noteworthy that under these circumstances of advanced undernutrition, a dose of only 1/3 of a unit of insulin on August 10 appreciably reduced the sugar in blood and urine, and a dose of ½ unit on August 11 abolished glycosuria (Table 29). The reality of this effect is shown by the fact that when insulin was omitted on the three following days, glycosuria returned in traces on August 12 and 13 and increased August 14, while the plasma sugar likewise rose. Normal plasma sugar was

attained with doses of 3 units (1 unit t. i. d.) on August 15 and 16, and treatment was then continued with doses of 1 unit daily. The subsequent details are given in paper No. 3 (Table 13).

The diet has been built up experimentally as high as 90 gm. protein, 200 gm. carbohydrate and 3800 calories, and the insulin dosage to 40 units as shown in the table mentioned. Further adjustments are being made. The weight has increased to 136 lb. and the strength is nearly normal. The patient is cheerful and trustworthy, is doing efficient work in the Institute, and gives indications of being able to earn his living outside.

Case No. 1075. (Juvenile diabetes. Death from gross violations of diet under insulin treatment.) Male. American. Age 14 years. Height 4 feet 10 inches. Weight 65 lb. at admission, Jan. 1, 1922. The case was of 2 years' duration, and the clinical condition was good. It was possible to build up a diet of 50 gm. protein, 10 gm. carbohydrate and 1000 calories, while maintaining normal plasma sugar. The only difficulty was the tendency to steal, which manifested itself not only in breaking diet but also in taking various small articles from other patients. He was discharged from the Institute April 2, 1922. Under the lax home conditions, diet was immediately broken, and the boy was returned to the Institute May 27, 1922, with heavy glycosuria again present. The tolerance had been injured, as it was possible this time to build up a diet of only 40 gm. protein, 5 gm. carbohydrate and 800 calories. The boy was kept in the Institute until Nov. 25, 1922, for purposes of training. He seemed to make a sincere effort to reform, and followed his diet in the Institute and promised to do so at home. To improve his condition and also aid in his fidelity, he was given 4 units of insulin per day, which permitted increasing the diet to 60 gm. protein, 20 gm. carbohydrate and 1400 calories. On this allowance the weight increased from 65 to 72 lb., and the appetite was satisfied according to the boy's own statement. He continued to take the insulin at home, but the father failed to report that he was again breaking diet and showing glycosuria. The next thing learned was that death occurred Dec. 23, 1922, with typical coma symptoms.

In this instance insulin did all that could be expected to promote fidelity by permitting the giving of enough food to prevent any hunger, but the character of the boy and his environment made any attempt at treatment hopeless.

Case No. 1081. (Mild diabetes with severe liver, kidney and heart disease. Use of insulin for increase of carbohydrate and total diet.) Male. Italian. Age 57 years. Height 5 feet 2½ inches. Weight 200 lb. maximum nine years ago, 146 lb. at admission, Feb. 10, 1922. No significant family history can be elicited except obesity. The patient is an Italian saloonkeeper, who can give little medical history except of pneumonia two years ago. He has used alcohol regularly and to excess for many years. He had anasarca at least as early as two years before admission, but considered his health all right until 1½ years ago, when he went to a physician because of weakness, polyphagia, thirst and polyuria, and glycosuria of 10 per cent. is said to have been found. This was easily

stopped by dieting for one week in hospital, but on discharge he disregarded diet and has had continuous glycosuria.

At admission, the patient had marked edema and ascites and showed the usual signs and symptoms of chronic kidney disease, atrophic cirrhosis of the liver, mitral regurgitation and cardiac decompensation. In addition, the teeth were extremely carious, and the left lower jaw was swollen and tender because of infection and necrosis of the mandible. The urine contained high percentages of sugar but not acetone, and showed also 13 gm. albumin per liter and many casts. Analyses of the blood plasma were as follows: sugar 681, chloride 606, urea 42 mg. per 100 cc. The blood pressure was 190 systolic, 110 diastolic.

The patient was very weak, cyanotic and dyspneic, lying in bed propped high on pillows, and a pleural tap was necessary to relieve his respiration. On a diet limited strictly to 30 gm. protein, without salt, the plasma sugar after four days fell to 0.159 per cent., and with the aid of digitalis the body weight was reduced to 133 lb. within the same period. The diet was then rapidly built up, and the patient was discharged March 4 on a salt-free diet of 70 gm. protein, 40 gm. carbohydrate and 1600 calories. The weight was 120 lb. without edema, and the blood pressure 150 systolic, 90 diastolic. It was arranged to continue the same diet in another hospital, to which the patient was referred for operation on his infected jaw. Under nitrous oxide, several teeth were removed and also a considerable portion of the left mandible, and recovery was rapid and uneventful.

On account of his ignorance, the patient soon suffered relapse, and on August 7 returned in nearly the same condition as before, weighing 140 lb. After similar treatment, he was discharged August 29, feeling fairly well at a weight of 115 lb.

A third admission was necessary on Nov. 1. This time glycosuria was absent and the plasma sugar only 0.169 per cent., indicating an attempt to follow diet, but anasarca had raised the weight to 152 lb. He was again discharged Nov. 20 improved and weighing 120 lb., as the result chiefly of salt-free diet with very little use of digitalis.

He was readmitted Jan. 21, 1923, in an extreme state at a weight of 160 lb. There was a trace of glycosuria, besides the same heavy albuminuria as always. The analyses of the plasma were: sugar 234, chloride 606, urea 100 mg. per 100 cc. The ascites was particularly large, and tapping was resorted to for the first time and repeated several days later, to relieve pressure on the heart and lungs. In addition to exclusion of salt, high protein was used in the attempt to promote diuresis, the diet being raised quickly to 100 gm. protein, 50 gm. carbohydrate and 2000 calories. This diet was also needed to give strength to the extremely weak and bedfast patient, and the general effect seemed to be beneficial, though the blood urea rose to a maximum of 196 mg. per 100 cc. on Feb. 8. With general clinical and circulatory improvement it fell slowly on the same diet to a minimum of 82 mg. on March 7 and rose to 130 mg. on March 17, and has remained within these limits.

Though the plasma sugar on the diet above mentioned was only 0.126 per cent. on March 2, the use of insulin was begun for a double purpose;

first, to observe any possible beneficial effect upon the liver or kidney disease; second, for certain more tangible advantages. One of these was the desirability of building up strength by a still more liberal diet if possible. In addition, it seems probable from well known studies of liver necrosis that a one-sided fat diet may be detrimental in liver disease, and that liberal carbohydrate feeding may have some protective action. Active diabetes, as manifested by hyperglycemia and glycosuria, seems to increase the vulnerability of all tissues, and the damaged liver might suffer to still greater extent if acidosis should develop. For these reasons, the diet was changed to 100 gm. protein, 250 gm. carbohydrate and 88 gm. fat, making 2200 total calories. With the aid of only 4 units of insulin per day, this diet is assimilated with plasma sugar no higher than 0.178 per cent. It is possible that the carbohydrate allowance may be made somewhat higher and the fat somewhat lower. No indication of a specific influence of insulin upon either the cirrhosis or the kidney disease has been observed, but the general nutrition is improved. The ascites has been controlled by the strict salt-free diet better than is possible with such a diet in most cases, and the peritoneal fluid remains moderate in quantity without further tapping. There is no edema elsewhere. The weight is 127 lb., the increase above the former minimum being partly a true gain of flesh. The patient is much more feeble than at his earlier admission, but nevertheless is able to be up and dressed during much of each day and to take short automobile rides. The prognosis is hopeless, but the temporary benefit from insulin seems to justify its use.

Case No. 1083. (Severe senile diabetes. Loss of tolerance from violations of diet estimated in terms of insulin. Improvement in both physical condition and fidelity.) Female. American. Age 67 years. Height 5 feet 1 inch. Weight 150 lb. maximum 12 years ago, 96 lb. at admission, March 10, 1922. The family history was unimportant, also the personal history except for tonsillitis in childhood and typhoid at 16 years. Twelve years ago, she was in bed four days with severe tonsillitis, and immediately afterward had an acute onset of thirst, polyuria, and loss of 26 lb. of weight in six weeks. No physician was consulted, and the symptoms remitted. She continued in fair health though with reduced weight and strength till one year ago, when intense thirst and polyuria returned and diabetes was diagnosed. Attempts at diet failed to control the condition, and progressive loss of weight and strength and an attack of neuritis forced her to enter the Institute.

The observations up to her discharge on May 19, 1922, established the case as severe, and tolerance was developed only to the extent of 50 gm. protein, 10 gm. carbohydrate and 900 calories. After several months of strict control at home and an increase to 1100 calories, the patient gradually became discouraged with her thin and weak condition and abandoned treatment. With the reappearance of symptoms, she became still weaker, and returned to the Institute for insulin treatment Nov. 29, 1922.

The weight was 95 lb. and heavy glycosuria and acetonuria were present on the former prescribed diet of 50 gm. protein, 10 gm. carbohydrate and 1000 calories. Three units of insulin daily were found necessary to

keep the glycosuria down to traces on this diet, indicating that tolerance to the extent of about 3 units of insulin had been lost during the few months of careless living. After gradual increases, the patient was dismissed Jan. 25, 1923, on 60 gm. protein, 40 gm. carbohydrate, 2000 calories, and 33 units of insulin per day. It has since been possible to increase this diet to 95 gm. protein, 85 gm. carbohydrate and 2600 calories, without increasing the insulin dosage. Under the care of a dietitian, the urine has remained uniformly sugar-free, and the last plasma sugar analysis was 0.148 per cent. during digestion. The weight has increased to 108 lb., with a corresponding gain of strength. The patient, encouraged by her improvement and liberal diet, remains entirely faithful to the treatment.

Case No. 1126. (Mild diabetes. Improved nutrition with small dosage of insulin.) Male. American. Age 36 years. Height 5 feet 6¾ inches. Weight 145 lb. maximum, 132 lb. at admission, April 17, 1922. The family history showed nephritis but no diabetes. Personal history—typhoid, mumps, and scarlet fever in childhood; tonsillitis followed by tonsillectomy, 1914. Symptoms of diabetes first appeared and the diagnosis was made with the attack of tonsillitis. Glycosuria was kept absent by restriction of carbohydrate only. During 1921, sugar freedom became difficult and the patient was careless. At one time the acidosis became somewhat threatening. He was referred to the Institute when free from glycosuria, for the planning of a diet on which he might remain so. The case proved to be mild, and he was discharged May 8 with constantly normal plasma sugar on a diet of 70 gm. protein, 35 gm. carbohydrate and 2000 calories, feeling entirely well at a weight of 125 lb.

Because of the patient's somewhat irregular habits in a hotel environment, this diet had to be reduced to 1800 calories. He was readmitted Sept. 11, 1922, for trial of the effect of insulin in a mild case. He had hyperglycemia of 0.150 per cent. before breakfast at a weight of 130 lb., as a result of exceeding the prescribed diet. With 2 units of insulin daily beginning Sept. 16, it became possible to increase the diet to 70 gm. protein, 50 gm. carbohydrate and 2400 calories, on which the patient was discharged Oct. 2 with plasma sugar of 0.092 per cent. He was readmitted Oct. 14 and the same conditions were found to obtain. After an increase of diet to 80 gm. protein, 70 gm. carbohydrate and 2700 calories, hyperglycemia gradually developed with the same dosage of 2 units of insulin. The patient returned home Oct. 31, weighing 135 lb. At home the diet has gradually been increased to 80 gm. protein, 80 gm. carbohydrate and 3200 calories. An increase of insulin to 10 units, divided in two injections per day, has become necessary to prevent glycosuria. The weight has risen to 138 lb., and the last plasma sugar analysis was 0.171 per cent. during digestion. The patient feels and looks much better, is better satisfied with his diet, and is able to take vigorous exercise which will probably use up his calories and prevent a need for much further increase of dosage.

Case. No. 1135. (Severe diabetes. Insulin requirement created by increased diet. Influence of fat.) Female. American. Age 25 years.

Height 5 feet 4 inches. Weight 90 lb. maximum, 68 lb. at admission, April 27, 1922. Family history negative, except for obesity and diabetes in an aunt and uncle. Personal history negative. The probable onset of diabetes was in July, 1920. Downward progress has been rapid on lax diet.

After admission, normal plasma sugar was obtained by a diet limited to 30 gm. protein for 9 days. She was discharged May 25, 1922, with a tolerance of 60 gm. protein, 10 gm. carbohydrate and 1100 calories, at a weight of 67 lb. Owing to minor errors at home, her diet there fluctuated between 1100 and 800 calories. She maintained her weight and was able to do a few hours of light work each day. Glycosuria was rare but hyperglycemia continuous, and the tolerance evidently fell considerably. She was readmitted Nov. 23, 1922, with a view to improving her nutrition with insulin.

The detailed record is given in paper No. 3 (Table 2). The low tolerance was indicated by the fact that hyperglycemia persisted for a week on a diet of 40 gm. protein, 5 gm. carbohydrate and 600 calories. At discharge, approximately the same hyperglycemia without glycosuria was present on 50 gm. protein, 10 gm. carbohydrate and 900 calories, with 8 units of insulin per day. It therefore appeared that in this patient an increase of the diet by 10 gm. protein, 5 gm. carbohydrate and 300 calories created an extra demand for insulin to the extent of 8 units.

The favorable progress continued at home, and in March the patient was taking 65 gm. protein, 45 gm. carbohydrate and 1800 calories, with 21 units of insulin per day. Glycosuria was absent and the last report of plasma sugar during digestion was 0.138 per cent. There has been an increase of weight to 80 lb. and more than a corresponding gain of strength.

Case No. 1156. (Mild juvenile diabetes. Direct and indirect benefits of insulin.) Male. Hebrew-American. Age 6 years. Height 3 feet 9 inches. Weight 43 lb. maximum and the same when first seen, May 22, 1922. Family history negative. Personal history—whooping cough at six weeks; severe lobar pneumonia at seven months, with otitis media and prolonged discharge after puncture of drum. Enuresis continued up to six months ago but then stopped entirely. May 15, extreme thirst was noticed, with polyuria and return of enuresis. After a few days, the boy was taken to the pediatrician whom the family ordinarily consulted, and the finding of glycosuria led to the call for a consultation.

The glycosuria was then heavy and the plasma sugar 0.550 per cent. A dietitian was placed in charge in the home, and a brief period of mild dietary restriction brought both urine and blood to normal. The diet was then rapidly built up to 60 gm. protein, 30 to 40 gm. carbohydrate and 800 to 900 calories. This seemed to be the limit of true tolerance, and attempts to raise the allowance to 1000 calories resulted in hyperglycemia. The weight was reduced only by 2 lb. and the strength was practically normal. Sometimes with a dietitian in charge and sometimes by the parents, the diet was carried out as faithfully as possible, but as this was an only child and he had been indulged greatly, there was serious

dissatisfaction that he should be at all below weight or should lose any of his ebullient spirits. Only the pediatrician's influence with the family held them to the treatment, and it is probable that they would before long have made a change to some physician who would have given the child a high diet even at the price of glycosuria.

In November, 1922, the use of insulin was begun under a specially trained dietitian at home. The small doses given at first showed little effect, and they were discontinued for three days on account of a rather violent skin eruption due to protein sensitiveness. They were then resumed without further trouble of this kind, and the diet and dosage were gradually increased. At present, the boy is taking 75 gm. protein, 70 gm. carbohydrate, 1900 calories, and 35 units of insulin daily. The weight has risen to 50 lb. Glycosuria now remains absent and the plasma sugar nearly normal. The diet is sufficiently abundant and varied to satisfy both the patient and his parents, and the possibility of normal weight and growth is the most pleasing feature. In such a case insulin proves highly important not only for the direct welfare of the child but also for the encouragement which it gives to the parents to continue careful treatment.

Case No. 1167. (Severe juvenile diabetes. Insulin requirement for fat. Apparent loss of tolerance with glycosuria during insulin treatment.) Female. Jewish American. Age 10 years. Height 5 feet 7 inches. Weight 67 lb. maximum, 57 lb. at admission, June 21, 1922. The family history was clear except for mild diabetes in a paternal grandfather. Except for whooping cough at 2 years, the patient was healthy until the acute onset of diabetes in April, 1922. The heavy glycosuria and dangerous acidosis cleared up in one week, but a diet of nothing but 10 gm. protein daily until July 18 was then necessary to obtain normal plasma sugar. Up to August 10, the limit of tolerance was no higher than 30 gm. protein, 2 gm. carbohydrate and 275 calories. With only 1 unit of insulin per day, diets of 60 gm. protein, 6 gm. carbohydrate and 804 calories and also of 60 gm. protein, 11 gm. carbohydrate and 374 calories were tolerated without glycosuria and with only moderate hyperglycemia. Addition of fat to make 1148 calories resulted in heavy glycosuria from September 10 to October 1, notwithstanding increase of insulin to 4 units daily. Heavy glycosuria then continued through the following weeks on a diet of 60 gm. protein, 10 gm. carbohydrate and 290 calories, while the insulin dosage was gradually increased to 14 units. This result apparently indicates a very marked loss of tolerance as the result of three weeks of high fat diet and attendant glycosuria.

The diet was subsequently raised as high as 60 gm. protein, 35 gm. carbohydrate and 1775 calories, for the assimilation of which approximately 28 units of insulin was required. This overnutrition program proved inexpedient to follow at home because of the impossibility of keeping glycosuria absent and at the same time avoiding hypoglycemic dangers with three doses of insulin per day, and the inexpediency of giving a midnight dose in this particular case. Accordingly, the diet has been reduced to 1000 calories, for which a dosage of 27 units per day is

still required. The weight has increased to 60 lb., and the strength is good though not fully normal. In view of the apparent susceptibility of this patient to downward progress with glycosuria, the only safe policy has seemed to be to keep symptoms under control as thoroughly as possible.

Case No. 1172. (Moderate diabetes with unusual gain of tolerance under diet treatment. Significance of hyperglycemia in terms of diet and insulin.) Female. American. Age 27 years. Height 5 feet 5¼ inches. Weight 130 lb. maximum, 76 lb. at admission, June 27, 1922. Family history negative. Personal history negative except for childhood diseases. Last Christmas she was in bed two weeks with a severe cold and fever. She felt weak afterward, and with the high diet ordered to build her up, thirst, polyuria and pruritus vulvae occurred. No diagnosis was made until April, when swelling of the feet led to urinalysis which showed glycosuria. She has since followed the dietary limitations prescribed but has seldom been free from glycosuria.

After admission, a diet of 30 gm. protein stopped glycosuria within three days, but further continuance for approximately two weeks was necessary to control the blood sugar. The diet was then built up to 55 gm. protein, 15 gm. carbohydrate and 1500 calories on August 5, and to 60 gm. protein, 20 gm. carbohydrate and 1600 calories on Nov. 5. The weight remained stationary at 74 or 75 lb., and the plasma sugar was constantly normal. The general strength was satisfactory, so that walks of several miles were taken daily, but nevertheless it was not up to a normal standard for work, and the patient's thin appearance was also a disadvantage. It was then found possible gradually to increase the diet to 70 gm. protein, 90 gm. carbohydrate and 2000 calories, this full limit being reached by the 1st of December. From then until the 1st of February no change occurred except that the plasma sugar before breakfast held a slightly elevated level between 0.146 and 0.156 per cent., and at the height of digestion as much as 0.250 per cent. was found without glycosuria. By the 1st of March, the fasting plasma sugar showed only a slight rise to 0.169 per cent. Then a sudden rise occurred to 0.203 per cent. on March 6 and 0.270 per cent. on March 8, when traces of glycosuria appeared. The weight was then 76 lb.

Instead of a reduction of diet, 2 units of insulin was given daily beginning March 11. Glycosuria ceased, but the plasma sugar on March 17 was still 0.200 per cent. Insulin was increased to 4 units on that date, to 6 units on March 25, and to 10 units on April 1. Hyperglycemia of 0.169 and 0.166 per cent. was still present on April 4 and 7 respectively. Further increases were made to 12 units on April 8 and to 16 units on April 17, while the diet was kept unchanged. By April 20 the plasma sugar was reduced to an approximately normal level of 0.128 per cent.

Case No. 1194. (Severe diabetes. Insulin requirement for protein, carbohydrate and fat. Improved physical and psychic condition.) Male. American. Age 32 years. Height 6 feet. Weight 145 lb. maximum, 100 lb. at admission, August 2, 1922. The family and personal histories were

unimportant. The patient had always been nervous and erratic, and was not very strong. Typical diabetic symptoms appeared acutely in August, 1918. The diagnosis was made six weeks later, by which time the weight had fallen to 120 lb. He gave up work and immediately entered a hospital, where glycosuria was cleared within three days by means of two complete fast days, followed by a low protein diet. Three weeks later he was discharged on a moderately high protein and fat diet, with restriction only of high carbohydrate foods. He followed diet carefully until February, 1919, improved in strength and gained weight to 143 lb.

In March, 1919, he returned to work. From this date to his admission on August 2, 1922, glycosuria was present constantly. He remained in a fair state of strength and health until December, 1919, and was able to carry on his business satisfactorily. His weight declined to 135 lb. The only other symptom was that he became fatigued easily.

In December, 1919, he was forced to retire on account of weakness and loss of weight. He then followed an accurately restricted diet until April, 1920, and regained strength. His weight increased from 120 lb. in December to 132 lb. in April. He then returned to work in May and continued actively engaged until September, 1921, when symptoms of acidosis developed, viz. drowsiness with nausea and vomiting. He was taken to a hospital, where acidosis subsided under fasting treatment. The weight by this time had fallen to 120 lb., and on account of exhaustion and weakness, it became necessary for him to remain in bed the greater part of the time.

From December, 1921, to May, 1922, he regained some strength but was unable to work. Glycosuria was heavy all the time and the urine contained considerable acetone.

From May, 1922, to the date of admission, he lost steadily in strength. He was drowsy and tired, and his breath was heavy with acetone. The appetite was very poor and constipation was severe. Styes developed on both lids in rapid succession and were troublesome from June to August of 1922. He became confined to bed in July on account of an abcess, which developed without known cause in the right thigh. Acidosis became more severe, accompanied by dyspnea and abdominal cramps. On one occasion coma seemed to be impending, but was averted by heroic measures. The patient was first seen in consultation at his home in Vermont on August 1. He was brought to the Institute by ambulance and train the following day, though the question existed whether he could survive the trip.

At admission, there was the usual heavy glycosuria and acetonuria. On a diet limited to 20 gm. protein and 5 gm. carbohydrate, glycosuria and acetonuria fell to traces by August 10, but the plasma sugar on the morning of August 9 was still 0.555 per cent. Surgical incision of the thigh abcess under nitrous oxide anesthesia on August 8 released about 300 cc. of thick pus, and was followed by complete healing within two weeks. The styes cleared up rapidly. Insulin treatment was begun August 10. The immediate effects of the first small doses are shown in Table 30. The hypoglycemic collapse occurring a few days later is discussed under

paragraph 6 of section 1 of this paper, and the detailed clinical and laboratory record is given in paper No. 3 (Table 12.).

This case was evidently not impossible to control by diet, but the tolerance and strength under unaided diet treatment must have remained extremely low. The patient is peculiarly nervous, at times extremely morbid and hysterical, and inclined to over-enthusiasm or over-despondency. He has made it clear to all concerned that he would be strictly faithful to treatment if there could be a hope of reasonable comfort and usefulness, but rather than accept an existence of extreme privation and invalidism he would deliberately discard treatment and eat to kill himself as rapidly as possible. With the aid of 54 units of insulin distributed in two or three doses daily, he was enabled to attain a diet of 100 gm. protein, 150 gm. carbohydrate and 3500 calories. Glycosuria still persisted, and it was evident that very high dosage would become necessary with further increase of weight. Reductions were therefore made, and at discharge on May 9 there was consistent freedom from glycosuria on a diet of 100 gm. protein, 100 gm. carbohydrate and 3000 calories, with 54 units of insulin per day, at a weight of 125 pounds. The patient is thoroughly pleased with the result, has improved in his nervous state, and has good hopes of returning to business life.

Case No. 1202. (Unexpectedly severe diabetes in middle life. Insulin requirement for increase of 1150 calories.) Female. American. Age 40 years. Height 5 feet 1¼ inches. Weight 142 lb. maximum, 90 lb. at admission, August 8, 1922. No diabetes, but several cases of obesity and hypertension in family. Personal history negative. Diabetes was discovered through onset of polydipsia in April, 1920. Glycosuria was controlled by diet, and in February, 1921, a cystic kidney was removed. The diet has been restricted in both carbohydrate and calories, but weight and tolerance have steadily been lost with frequent returns of glycosuria.

At admission, there was no ketonuria, and glycosuria was easily stopped within two days. The case at first appeared mild, but unexpected difficulty was encountered in building up tolerance. At discharge, Sept. 30, 1922, it was necessary to limit the diet to 45 gm. protein, 5 gm. carbohydrate and 650 calories at a body weight of 86 lb. Hyperglycemia of 0.166 per cent. was present on this diet, and all attempts to increase food had led to greater hyperglycemia or glycosuria. It was arranged that the patient should continue this undernutrition diet at home, and if the tolerance did not rise she should return later to receive insulin.

The diet was somewhat exceeded at home, and the patient returned Feb. 15, 1923, weighing 88 lb., with hyperglycemia and slight glycosuria but no acidosis. Increasing diet and insulin were given for three weeks, so that at discharge, March 7, 1923, the patient was taking 80 gm. protein, 50 gm. carbohydrate and 1800 calories, with 16 units of insulin divided in two injections per day, at a weight of 95 lb. At home, the insulin has been increased to 18 units to control hyperglycemia and traces of glycosuria. The adjustment is still not complete, but it seems probable that approximately 20 units of insulin may be required to balance an increase

of 35 gm. protein, 45 gm. carbohydrate and 1150 calories in this patient's diet.

Case No. 1212. (Very severe diabetes past middle life. Insulin requirement for increased calories. Transformed prognosis.) Female. American. Age 50 years. Height 5 feet 3¼ inches. Weight 148 lb. maximum in 1919, 78 lb. at admission, August 19, 1922. Family history negative. Except for measles in childhood and 2 miscarriages 15 years ago, the patient was thoroughly well until the onset of diabetic symptoms in 1919. Glycosuria ceased with two days of fasting. She gradually abandoned diet and has had continuous glycosuria, until extreme decline of weight and strength forced her to enter the Institute.

The severity of the case is shown by the detailed record in paper No. 3 (Table 10). Though glycosuria ceased after 13 days of semi-starvation, the plasma sugar persisted at a level which would have been attended with marked glycosuria except for the marked renal impermeability. The initial body weight of 78 lb. was raised as high as 95 lb. by edema. Five weeks of extreme undernutrition having failed to reduce the blood sugar, insulin was begun in dosage of 1 unit per day, and in one week the plasma sugar fell from 0.334 to 0.180 per cent. The diet and dosage were gradually increased until the patient was discharged Dec. 16, 1922, on 50 gm. protein, 15 gm. carbohydrate, 1200 calories and 20 units insulin daily. The body weight was 86 lb. without edema, and the strength was greatly improved though not normal. By Feb. 20 the insulin dosage had been increased to 25 units to prevent glycosuria from appearing on the 1200 calory diet. With diet treatment alone, it is improbable that this patient could have been kept free from glycosuria, and her loss of weight and strength must have continued to an early death. The prognosis is now transformed as regards not only life but also strength, comfort and usefulness.

Case No. 1214. ("Total" diabetes. Recovery from coma with insulin. Psychosis. Diminished severity of diabetes.) Male. American. Age 18 years. Height 5 feet 10 inches. Weight 138 lb. maximum in 1920, 113 lb. at admission, August 23, 1922. The family history was said to be negative for diabetes, obesity or other hereditary disorders. Later it was learned that a very marked strain of insanity in the family had been intentionally concealed. The patient had measles and whooping cough in early childhood. His entire life was spent in a rural district of South Carolina, and he is said to have had chills and fever, supposedly representing a mild malaria, in most summers since the age of 4 years. Otherwise he has been well and strong, and has been free from excesses in food or other habits.

The present trouble was first noticed through slight loss of weight in 1918. Glycosuria of 7.2 per cent. was found, but was cleared up by two weeks of diet in hospital. The patient thought himself entirely well and ate liberally, so that his weight increased and sugar returned. Glycosuria has continued, and in two subsequent hospital treatments (the second in

TABLE 7
Case No. 1214

Date	Diet				Urine					Blood		Weight Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.	Total Acetone Gm.	NH_3 Gm.	Nitrogen Gm.	Sugar Gm.	D:N Ratio	Plasma Sugar Mg per 100 cc.	CO_2 Vol. %		
1922													
Aug.													
23	30	4	0	156	....	....	....	....	....	469	61.2	113	....
24	30	12	0	228	....	....	....	....	....	....	....	....	....
25	30	17	0	273	....	....	....	+++	....	....	....	110	....
26	"	"	"	"	....	....	....	+++	....	....	....	....	....
27	20	13	0	197	....	....	....	+++	....	....	....	....	....
28	20	11	0	179	....	....	....	+++	....	536	....	111	....
29	20	9	0	161	....	....	....	+++	....	....	....	....	....
30	"	"	"	"	....	....	....	+++	....	....	....	109	....
31	"	"	"	"	....	....	....	+++	....	577	....	....	....
Sept.													
1	"	"	"	"	....	....	6.36	21.15	3.32	....	....	109	....
2	"	"	"	"	....	....	7.58	28.27	3.72	....	....	....	....
3	"	"	"	"	....	....	8.54	27.25	3.19	....	....	108	....
4	"	"	"	"	....	....	8.35	26.64	3.19	652	58.3	....	....
5	"	"	"	"	....	....	8.11	26.88	3.31	....	....	109	....
6	"	"	"	"	....	....	7.94	27.40	3.45	....	....	....	....
7	"	"	"	"	....	....	6.50	17.29	2.66	....	....	109	....
8	"	"	"	"	....	....	6.82	17.41	2.55	....	....	....	....
9	"	"	"	"	....	....	6.66	17.79	2.67	....	....	110	....
10	"	"	"	"	....	....	7.09	19.76	2.78	....	....	....	....
11	70	124	0	1400	....	....	9.73	35.20	3.62	....	....	109	....
12	"	"	"	"	....	....	9.93	32.16	3.23	....	....	....	....
13	"	"	"	"	5.07	....	9.31	34.00	3.65	577	....	109	....
14	"	"	"	"	2.76	....	6.12	26.64	4.35	....	....	....	....
15	"	"	"	"	8.10	....	9.13	38.56	4.22	484	59.5	110	....
16	"	"	"	"	8.98	....	7.23	24.10	3.33	....	....	....	....
17	"	"	"	"	8.30	....	9.15	30.32	3.31	....	....	109	....

18	70	124	0	1400	8.98	....	9.15	36.93	4.03	555	....	....	....
19	"	"	"	"	9.96	....	9.85	37.74	3.83	....	....	109	....
20	"	"	"	"	13.37	....	11.05	45.46	4 11	....	....	....	....
21	"	"	"	"	10.51	....	12.28	....	....	....	....	107	....
22	"	"	"	"	....	3.56	9.83	36.29	3.69	625	....	....	....
23	"	"	"	"	....	3.71	10 89	34.25	3.15	577	41.4	105	....
24	70	124	40	1560	....	2.50	10.30	65.20	2.44	....	....	....	....
25	"	"	"	"	....	2.63	10.32	51.63	1.12	....	....	104	....
26	"	"	"	"	....	3.79	10.52	74.30	3.22	625	....	....	....
27	"	"	"	"	....	3.62	9.23	77.35	4.01	....	....	103	1
28	"	"	"	"	....	4.80	10.51	76.13	3.43	....	....	....	2
29	"	"	"	"	....	3.76	10.91	77.90	3.09	484	44.3	105	2
30	"	"	"	"	....	....	12.64	85.01	3.56	....	....	....	2
Oct.													
1	"	"	"	"	....	5.43	12.74	75.90	2.81	....	40 4	105	2
2	"	10	"	530	....	4.37	11.83	79.32	3.32	600	43 3	....	2
3	"	"	"	"	....	3.74	13.67	67.18	1.98	....	....	106	2
4	"	"	"	"	....	3.83	11.71	67.18	2.32	....	....	....	2
5	"	"	"	"	16.76	3.60	12.21	66.61	2.17	....	....	107	2
6	"	"	"	"	19.75	3.83	13.25	61.04	1.58	....	....	....	2
7	"	"	"	"	....	2.75	13.57	....	....	885	....	106	2
8	Fast				18.59	2.00	9.19	50.97	(5.54)	....	53.8	....	2
9	Fast				11.05	2.52	8.34	44.64	(5.35)	577	....	104	2
10	Fast				10.61	3.08	9.19	53.22	(5.79)	....	....	....	2
11	Fast				7.67	2.65	7.61	38.72	(5.08)	....	....	104	2
12	Fast				6.66	1.61	8.06	33.08	(4.10)	536	....	....	2
13	Fast				11.26	2.91	8.98	50.17	(5.58)	....	....	104	2
14	Fast				8.96	2.93	8.38	47.90	(5.71)	....	....	....	4
15	Fast				6.82	2.86	8.91	33.36	(3.74)	577	....	....	4
16	Fast				6.73	1.78	7 26	43.60	(6.00)	....	....	104	4
17	Fast				9.91	....	5.96	38.89	(6.52)	....	....	....	4
18	Fast				15.80	....	6.73	46.14	(6.85)	....	....	100	0
19	30	26	10	....	4.35	3.12	8.26	30.73	....	652	41.6	....	32
	45	73	15	During	night.								
20	70	102	0	1200	18.46	2.90	12.09	65.36	(5.40)	455	....	100	0
21	"	"	"	"	17.14	3.12	16.62	72.96	(4.38)	544	32.8	....	0
22	"	"	"	"	18.43	4.06	16.21	68.83	(4.24)	625	....	....	0
23	60	64	60	1056	....	3.45	15.05	76.03	1.06	....	16.6	....	20

TABLE 7.—*Continued*

Date 1922	Diet				Urine					Blood		Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.	Total Acetone Gm.	NH_3 Gm.	Nitrogen Gm.	Sugar Gm.	D:N Ratio	Plasma Sugar Mg. Per 100 cc.	CO_2 Vol. %		
Oct.													
24	60	0	60	480	6.54	3.37	13.99	78.59	1.32	588	81.5	....	40
25	"	"	"	"	4.58	4.76	10.68	46.19	....	428	86.2	....	40
26	"	2	"	498	+	1.93	12.55	19.76	....	429	....	....	40
27	"	"	"	"	+	0.80	8.19	10.76	....	375	....	....	40
28	"	60	"	1020	+	0.22	4.90	+	....	195	80.4	....	20
29	"	113	"	1500	+	0.90	6.00	20.60	....	405	78.6	....	15
30	"	"	"	"	+	0.72	6.08	8.22	....	312	69.1	....	15
31	"	"	"	"	++	0.29	1.00	2.30	....	258	....	....	20
Nov.													
1	"	"	"	"	++	0.67	9.29	5.67	....	263	76.7	....	5
2	"	"	"	"	++	1.40	12.31	51.88	....	349	....	....	0
3	"	"	"	"	++	0.28	8.53	23.37	....	....	....	....	0
4	"	"	"	"	++	0.58	7.90	13.68	....	357	....	....	0
5	"	"	"	"	++	0.17	9.22	11.13	....	....	....	....	0
6	"	"	"	"	++	1.26	7.10	41.88	....	....	....	....	0
7	"	"	"	"	++	0.99	7.03	29.49	....	....	....	....	0
8	"	"	"	"	+++	1.00	9.29	37.85	....	416	....	....	0
9	"	"	"	"	+++	3.03	11.75	46.08	....	375	....	....	0
10	"	"	"	"	+++	....	8.79	74.67	....	....	....	....	0
11	"	"	"	"	+++	1.66	7.81	93.00	....	....	....	....	0
12	"	"	"	"	++	....	10.00	35.77	....	441	78.6	....	0
13	"	"	"	"	+	....	....	+	....	455	72.9	....	12
14	"	"	"	"	0	....	....	0	....	....	....	....	12
15	"	"	"	"	0	....	....	0	....	....	....	....	12
16	"	"	"	"	0	....	....	0	....	....	....	....	20
17	"	"	"	"	0	....	....	0	....	100	57.6	....	20
18	"	"	"	"	0	....	....	0	....	....	....	....	20
19	"	"	"	"	0	....	....	0	....	75	....	....	20

May, 1922) it failed to clear up. He came to the Institute because of this difficulty and the progressive emaciation and weakness.

Except for slight thinness, the physical examination was negative. The mental state seemed normal, though the patient was of rather low intelligence and was much worried about himself. The usual heavy sugar and acetone reactions were present, but there were no indications that the case was at all unusual in severity, and treatment was begun in routine manner.

The continuance of heavy sugar and acetone reactions for ten days, on a diet limited first to 30 gm. and then to 20 gm. protein, gave warning of an unusually serious condition. Urinalyses then disclosed "total" diabetes, which remained unaffected by the prolonged undernutrition shown in the table. Presumably on account of this undernutrition, the absolute quantities of sugar, nitrogen and acetone excreted were only moderate. Also, the plasma bicarbonate was never subnormal, and clinically there were neither acidosis symptoms nor extreme weakness.

On September 11, however, after three weeks of almost complete starvation, it became evident that nothing was being accomplished. Accordingly, a carbohydrate-free diet of 70 gm. protein and 1400 calories was begun. Coming after the period of extreme undernutrition, this seems to have produced a slightly positive nitrogen balance, even though the D:N ratios remained maximal. The clinical condition grew worse more rapidly on this diet than on the semi-starvation, as respects both loss of strength and acidosis symptoms. From 59.5 vol. per cent. before the high fat diet, the plasma bicarbonate by Sept. 23 had fallen to 41.4 vol. per cent., and fatal danger seemed to be no more than a very few days distant.

Accordingly, beginning September 24, 40 gm. carbohydrate was added to the diet, raising the calories to 1560 daily. A slight and temporary retention of sugar occurred, as shown by the fall in D:N ratios for September 24 and 25, but the maximal ratios then returned. The clinical condition was no better, and as there was no hope in either high or low diet, the question of using insulin became acute.

This question was a very difficult one at this time, because of the number of patients with desperately severe diabetes whose survival apparently depended upon the very scanty supply of insulin. All were being kept on minimal doses, and a number of other patients in only slightly less serious danger could not yet be given insulin. None had been given to the present patient because it was believed that the severity of the condition was such that any appreciable control of it would require dosage so large as to be unobtainable except by deprivation of others. The treatment was therefore a battle against time, in the attempt merely to preserve life until the supply of insulin should increase. The attempt was plainly failing, and it became imperative to seek what benefit might be found in small doses of insulin.

Therefore, after a preliminary dose of 1 unit on Sept. 27, regular dosage of 2 units daily was begun, divided into 1 unit at morning and 1 unit at evening. No effect was perceptible. The high D:N ratio of Sept. 27

probably indicated a sweeping out of carbohydrate retained from Sept. 24 and 25, and the nitrogen balance began to turn toward the negative side. The plasma sugar on the whole was no lower than before, and the plasma bicarbonate from Sept. 29 to Oct. 2 was only slightly above 40 vol. per cent.

The one remaining possibility was to reduce the demand for insulin and at the same time reduce acidosis by undernutrition. Therefore, from Oct. 2 to 7 the protein was kept at 70 gm. and the carbohydrate at 40 gm., but the fat intake was cut to 10 gm., making the total calories 530 daily. Under these conditions, the D:N ratio fell slightly, and the plasma bicarbonate by Oct. 8 had risen to 53.8 vol. per cent. without alkali administration. Acidosis symptoms were absent, though the urinary acetone excretion had not particularly changed.

At the same time it was evident that the diabetes was still not far from maximal, the nitrogen balance was negative, weight was being lost to an extent which was somewhat masked by water retention, and acidosis might again become threatening at any time. Experience has proved that all these dangers are lessened if the diabetes can be brought under control, even by absolute fasting. Fasting was therefore imposed for the 11 days, Nov. 8 to 18. Correct D:N ratios for this period would be of interest, but those obtained are placed in parenthesis to indicate their fictitious character. Soup and other sources of nitrogen were avoided, but it was necessary during the fasting period to give large quantities of other "fillers." There is little to suspect from the mineral oil, agar jellies and celluflour. The thrice-cooked vegetables were carefully prepared, and the bran biscuits were made of bran extracted by three boilings, and India gum. The flavoring extracts, of which undernourished patients are so fond, were synthetic and sugar-free, but their aldehydes and other ingredients may be suspected as sources of sugar. On the whole, it is entirely possible that a bulky diet of this character will yield 10 to 20 gm. of glucose forming material per day and this fact must be considered as proved by the D:N ratios. The main point is that these ratios remained very high even when it became possible on Oct. 14 to increase the daily insulin dose to 4 units.

Because of postal delay, no insulin was available on Oct. 18. By the next morning the patient was almost in coma, with very low plasma bicarbonate and alarming clinical signs. Food was given, also 5 gm. sodium bicarbonate by mouth, and, the insulin having arrived, 32 units of it had to be used within six hours to avert the imminent danger. Glycosuria was thus reduced to traces for a few hours and acetonuria nearly abolished, but both rapidly returned. In consequence of the large dose, no insulin could be given on Oct. 20, 21 and 22, during which time a carbohydrate-free diet of 70 gm. protein and 1200 calories was tried.

On the afternoon of Oct. 23, without warning, the patient had a general epileptiform convulsion, and following it passed into what appeared to be typical diabetic coma, with dyspnea and with a reduction of plasma bicarbonate to 15.7 vol. per cent. Increased supplies of insulin arrived on this day. Beginning with the patient in profound unconsciousness at

5 P. M., the giving of 20 units before midnight and 40 units on the following day cleared up the coma. With the aid of only 30 gm. of sodium bicarbonate, the CO_2 capacity of the plasma rose to 81.5 vol. per cent. in less than 24 hours. Glycosuria persisted with this dosage, on a diet of 60 gm. protein and 60 gm. carbohydrate with or without fat, until Oct. 28. The dosage was then reduced to 20 and 15 units, and glycosuria persisted irregularly. Sodium bicarbonate in dosage of 15 gm. daily was continued to Oct. 28 and then stopped.

The convulsion of Oct. 23, which occurred before the coma and before the giving of insulin or bicarbonate on that day, was said to have been the first in the patient's entire life. Following recovery from the coma, he appeared slightly peculiar mentally, but the condition was attributed to weakness. The mental aberration increased from day to day, and another violent convulsion occurred on Oct. 27, and several more major and minor ones during the following two days. From Oct. 28 onward the patient was completely disoriented as to time, place and persons, had all sorts of transitory illusions and delusions, talked or mumbled much of the time, and was sometimes incontinent of urine and feces. Means were taken for urine collections, though the figures for analyses after this time may not always be exact. All the insulin since Oct. 24 had been divided into four equal doses for each 24 hours, given six hours apart. Up to Oct. 31, slight glycosuria and acetonuria persisted with the dosage of 15 or 20 units per day, on a diet of 60 gm. protein, 60 gm. carbohydrate and 1500 calories.

As the insulin doses mentioned were considered large at that time, the question arose whether they could have contributed to the mental impairment. Accordingly, the same diet was continued, while insulin was omitted until Nov. 13. The patient remained extremely weak, bedfast, and unchanged in mental state, though no convulsions occurred after Oct. 29. Next, in order to learn whether the condition could be helped by control of the diabetes and improvement of nutrition, insulin was resumed on Nov. 13 in dosage of 12 units, which stopped the glycosuria, and increased on Nov. 16 to 20 units, which for the first time reduced the blood sugar to normal. The mental trouble seemed to be in no way improved.

Two practical problems had now to be considered. One was the propriety of using considerable doses of insulin for a patient who seemed hopelessly insane, when the entire supply was urgently needed by other patients. The other was the advisability of removing the patient to an institution having better facilities for his psychiatric care. Under arrangements made by the family, the patient was transferred on Nov. 20 by ambulance and train to the Johns Hopkins Hospital, where he arrived safely notwithstanding his extremely weak state. Reports received state that he was treated there first without insulin and later with insulin, and that he slowly improved not only physically but also mentally, but more recently he has suffered a relapse mentally.

The two most puzzling questions in connection with the case can be answered only speculatively. One pertains to the nervous disorder. The convulsions can scarcely be attributed to either insulin or bicarbonate,

since the first one occurred before either remedy was used. The mental trouble can best be regarded as a diabetic psychosis, further induced by the state of extreme malnutrition, in a patient predisposed by heredity. The occurrence of both physical and mental improvement gradually under further insulin treatment tends to support this view and to remove any suspicion concerning insulin.

The second question concerns the apparent improvement in the diabetic condition at the end of October, simultaneously with the psychosis. There is no ground for attributing any lasting curative effect to the large insulin doses used at this time. The fact remains that the diabetes assumed a much milder form. After Nov. 1, there was actually a positive carbohydrate balance without insulin. When insulin was resumed on Nov. 13, 12 units sufficed to abolish glycosuria, and 20 units would evidently have proved an excessive dose if continued. Three explanations are possible. One is the state of extreme emaciation and cachexia. The patient was bedfast, too weak to be weighed, and this condition might tend to suppress glycosuria and accentuate the effects of insulin. This explanation, however, would not hold for a continued mildness of the diabetes while the patient was regaining weight and strength. A second hypothetical explanation is that the patient was suffering from a subacute pancreatitis. An infection of this kind might explain the great severity of the case, and at the same time might contribute somewhat toward the etiology of the convulsions and psychosis. Subsidence of the infection, either spontaneously or with the aid of the improved resistance resulting from the high insulin dosage, might permit the diabetes to resume its previous comparatively mild course. The third explanation must be that a functional element is involved even in "total" diabetes, so that some recovery of tolerance is possible when the function is adequately spared. Certain former evidence points to this same conclusion.

Case No. 1240. (Obesity and mild diabetes, complicated suddenly by sepsis and coma. Fatal result with inadequate doses of insulin.) Male. American. Age 43 years. Seen in consultation September 24, 1922. The family were obese, and there was a history of several cases of hypertension and apoplexy and one carbuncle. The personal history was negative except for obesity and enormous over-eating. With a height of 5 feet 7 inches, the highest weight was 235 lb., and a gradual loss has occurred to 209 lb. For an indefinite number of years the patient has ignored his known diabetes and been comfortable and vigorous. About September 15 he called his family physician for a boil on the right side of the neck behind. Because of the heavy glycosuria, the physician and a consulting surgeon took all precautions. The patient was placed immediately in a hospital on an accurate fat-free diet of about 30 gm. protein and 60 gm. carbohydrate daily. The boil was freely opened and drained, but the infection spread rapidly. On September 20 a second operation was performed, opening the neck from one mastoid process to the other, with verticle incisions to allow free lifting up of the flaps. A hard, dusky infiltration has nevertheless advanced forward over the left clavicle. The temperature has been 102 to 103 degrees F., leukoctytes 17,000 with 97

per cent polymorphonuclears, and glycosuria and acidosis have increased alarmingly notwithstanding diet and soda.

The patient when seen was still surprisingly strong and cheerful, only moderately dyspneic, and unaware of the full seriousness of his condition. As all the standard methods had apparently been used to the best advantage, it was only a question whether insulin might save life by controlling the sugar and the acidosis and at the same time raising the resistance to infection. Only 40 units had been brought along for the purpose, partly because this was all that could be spared and partly because we were not yet aware of the huge dosage necessary in such cases. These 40 units were given in 5-unit doses hourly during the night, and an additional 35 units obtained by mail permitted continuance of the treatment the next day. The plasma sugar, which was 0.885 per cent. before the first dose at 6:45 P. M., was gradually reduced to 0.544 per cent. by 7 o'clock the next morning. The CO_2 capacity of the plasma rose from a minimum of 13.7 volumes per cent. to 46.2 volumes per cent., but this rise is sufficiently explained by the bicarbonate dosage. Glycosuria continued heavy, and the acetone of blood and urine was not appreciably changed. All symptoms grew worse during September 25, and death occurred from sepsis and coma at 11 A. M. September 26.

This case may have been hopeless under any conditions, but the entirely inadequate supply of insulin available makes this an unsatisfactory test.

Case No. 1238. (Early stage of juvenile diabetes. Rapid downward progress estimated in terms of insulin. Insulin requirement for carbohydrate and protein additions. Improved nutrition.) Female. American. Age 2½ years. Height 3 feet. Weight 27 lb. maximum and at admission, Sept. 25, 1922. Family history negative. Personal history negative except whooping cough at 1 year and sore throat once. In June, 1921, had 7 large boils. Thirst and polyuria in August led to diagnosis on August 26, 1921. Glycosuria ceased in 24 hours with simple carbohydrate restriction and remained absent for two weeks. Diet and tests were then stopped, on the assumption that the condition had been transitory. The child continued in apparently perfect health until thirst and polyuria returned within the last few weeks, and heavy glycosuria was again discovered.

At admission, the child appeared entirely well, and the urine and blood quickly returned to normal. She was discharged Oct. 29, 1922, weighing 26 lb. on a diet of 35 gm. protein, 5 gm. carbohydrate and 500 calories, as 600 calories had proved slightly beyond her tolerance.

Favorable progress at home led to an increase of diet to 600 calories, which gradually gave rise to glycosuria. The parents failed to bring the condition under control, and glycosuria and loss of weight became more marked. The child was readmitted Dec. 30, 1922, for insulin treatment. The weight at this time was 24 lb. and the appearance and strength were distinctly poorer.

The detailed record is given in paper No. 2 (Table 3). It will be noticed that the diet from Jan. 29 to Feb. 8 was 40 gm. protein, 10 gm. carbohydrate and 600 calories, which was approximately the upper limit

of the child's former tolerance. Daily dosage of 12 units of insulin was necessary for assimilation of this diet without glycosuria but with marked hyperglycemia. It may be estimated, therefore, that in less than two months this small child had deteriorated in insular function to the extent of 12 units per day.

The patient was discharged March 11, 1923, at her original weight of 27 lb., on a diet of 60 gm. protein, 75 gm. carbohydrate and 1000 calories, with 20 units of insulin divided in three injections per day. She was free from glycosuria though the plasma sugar showed the usual tendency to high morning and low evening figures. The liberal carbohydrate was allowed in order to give some approximation to the normal composition of the infantile diet, and the high calories in proportion to weight were given with a view to favoring growth, which had been stationary since her first admission. Several hypoglycemic reactions were experienced on March 22 and 23 and the extract was reduced to 15 units and further to 12 units on April 3rd for the same reason. Glycosuria remains absent. The body weight has increased to 30 lb.

Case No. 1244. (Severe diabetes. Healing of perforating ulcer. Large influence of added calories compared with small influence of added carbohydrate in terms of insulin dosage. Influence of body weight.) Female. American. Age 48 years. Height 5 feet 5⅜ inches. Weight 130 lb. maximum seven years ago, 78 lb. at admission, October 3, 1922. Family and personal history negative. Existence of diabetes has been known for six years. Treatment has been efficient but glycosuria has repeatedly returned owing to severity of case. She was referred to the Institute chiefly in the hope of insulin treatment.

Physical examination was negative except for emaciation and a small sinus which discharged pus between the fourth and fifth toes of the right foot, and into which a probe could be passed for nearly an inch. Owing to previous undernutrition treatment, ketonuria was absent and glycosuria moderate. On a diet limited to 25 gm. protein, the urine became clear in three days, and in one week the plasma sugar fell from its original level of 0.385 to 0.085 per cent. An increase of diet to 40 gm. protein, 3 gm. carbohydrate and 700 calories raised the plasma sugar within two days to 0.223 per cent., illustrating the usual difference between semi-starvation and something less than a "basal" diet in a severe case. A diet of 500 calories was tolerated for a week, after which an increase to 40 gm. protein, 5 gm. carbohydrate and 1000 calories gave rise to hyperglycemia of 0.349 per cent. and traces of glycosuria in three days. Reduction to 600 calories lowered the plasma sugar only to 0.254 per cent., and insulin treatment was therefore begun Oct. 29.

With the same diet of 40 gm. protein, 5 gm. carbohydrate and 600 calories and only 1 unit of insulin daily, the plasma sugar fell in two days to 0.104 per cent. A gradual increase to 55 gm. protein, 15 gm. carbohydrate and 1300 calories with continuance of the 1 unit dosage (½ unit morning, ½ unit evening) up to Nov. 11 resulted in hyperglycemia and glycosuria. These continued with gradual increase of the dosage to 6 units on Nov. 15, and only ceased with an increase to 8 units

TABLE 8

Case No. 1244

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Oct.								
29	40	46	5	600	+	254	...	1
30	"	"	"	"	0	...	...	1
31	"	"	"	"	0	104	70	1
Nov.								
1	50	62	10	800	0	...	...	1
2	50	84	10	1000	0	...	73	1
3	"	"	"	"	0	112	...	1
4	55	113	15	1300	0	...	70	1
5	"	"	"	"	0	...	...	1
6	"	"	"	"	0	...	69	1
7	"	"	"	"	+	268	...	1
8	"	"	"	"	+++	...	72	1
9	"	"	"	"	++++	288	...	1
10	"	"	"	"	+++	..	72	1
11	"	"	"	"	++	..	...	1
12	"	"	"	"	++	..	72	2
13	"	"	"	"	++++	...	...	2
14	"	"	"	"	+++	...	73	2
15	"	"	"	"	++++	270	...	6
16	"	"	"	"	++	...	73	6
17	"	"	"	"	+++	...	...	6
18	"	"	"	"	++++	257	75	6
19	"	"	"	"	+	...	...	6
20	"	"	"	"	+	...	75	6
21	"	"	"	"	0	...	...	6
22	"	"	"	"	+	...	74	4
23	"	"	"	"	+	...	..	8
24	"	"	"	"	0	...	...	8
25	"	"	"	"	0	153	70	8
26	"	"	"	"	0	...	70	8
27	"	"	"	"	0	140	..	8
28	"	"	"	"	0	...	71	4
29	"	"	"	"	0	...	...	4
30	55	135	15	1500	0	...	68	8
Dec.								
1	"	"	"	"	0	130	...	8
2	"	"	"	"	0	...	72	8
3	"	"	"	"	0	...	...	8
4	"	"	"	"	0	108	74	8
5	"	"	"	"	0	...	...	8
6	55	137	35	1600	0	...	76	6
7	"	"	"	"	0	...	...	8
8	"	"	"	"	0	125	76	8
9	"	"	"	"	0	...	...	8
10	"	"	"	"	0	122	73	0
11	"	"	"	"	0	...	...	6
12	"	"	"	"	0	...	74	8
13	"	"	"	"	0	...	...	8
14	"	"	"	"	0	...	73	8
15	"	"	"	"	0	...	...	8
16	"	"	"	"	0	203	73	8
17	"	"	"	"	0	...	...	8

TABLE 8.—*Continued*

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Dec.								
18	55	137	35	1600	0	...	74	8
19	"	"	"	"	0	...	...	8
20	"	"	"	"	+	139	74	8
21	"	"	"	"	0	...	...	8
22	"	"	"	"	0	...	76	8
23	"	"	"	"	0	115	...	8
24	"	"	"	"	0	...	75	8
25	"	"	"	"	0	...	...	8
26	"	"	"	"	0	...	68	8
27	"	"	"	"	0	...	...	8
28	"	"	"	"	0	...	76	8
29	"	"	"	"	0	175	...	8
30	"	"	"	"	0	...	76	8
31	"	"	"	"	0	...	...	8
1923								
Jan.								
1	"	"	"	"	0	...	79	8
2	"	"	"	"	+	168	...	8
3	"	"	"	"	0	...	74	8
4	"	"	"	"	0	182	...	8
5	"	"	"	"	0	...	76	8
6	"	"	"	"	0	...	...	8
7	55	182	35	2000	0	...	77	8
8	"	"	"	"	0	...	...	8
9	"	"	"	"	0	...	76	8
10	"	"	"	"	0	189	...	8
11	"	"	"	"	0	...	76	8
12	"	"	"	"	0	...	...	8
13	"	"	"	"	0	...	77	8
14	"	"	"	"	0	242	...	8
15	"	"	"	"	0	...	77	8
16	"	"	"	"	0	...	...	8
17	"	"	"	"	++	288	77	8
18	"	"	"	"	0	...	...	12
19	"	"	"	"	0	...	77	12
20	"	"	"	"	0	258	...	12

following Nov. 23. The body weight meanwhile had fallen to 70 lb. It seems evident that the relatively small increase in glucose value of the above diet is inadequate to account for the difference between 1 unit and 8 units of insulin, and that the greatly increased requirement for insulin must be explained chiefly by the increased calories of the diet. The observation permits, at least, the mathematical expression that the assimilation of an added 15 gm. protein, 10 gm. carbohydrate and 700 calories required 7 units of insulin in this patient.

The plasma sugar remained normal mornings and evenings on the program mentioned until Dec. 5. A slight increase of diet to 55 gm. protein, 35 gm. carbohydrate, and 1580 calories then produced no perceptible

change up to Dec. 23, when the plasma sugar was still 0.115 per cent. It is noteworthy that this addition of 20 gm. carbohydrate had such trivial influence in comparison with the previous increase of total calories. By Jan. 4, 1923, the plasma sugar had risen gradually to 0.182 per cent., probably in connection with the gradual increase of weight to 74 lb. rather than with the carbohydrate addition mentioned. The diet was then raised to 2000 calories by addition of fat, leaving the protein at 55 gm. and the carbohydrate at 35 gm. By Jan. 17 the weight had risen to 77 lb. and the plasma sugar to 0.288 per cent., and glycosuria appeared. Increase of insulin to 12 units daily then abolished glycosuria but not hyperglycemia. The patient was discharged Jan. 20.

The sluggish ulcer in the foot began to granulate better under diet treatment and healed slowly and completely under insulin treatment. The general condition was tremendously improved by the liberal diet made possible by insulin. At home, a gradual increase has been made to 80 gm. protein, 45 gm. carbohydrate, 2200 calories and 21 units of insulin, divided in three injections daily. The weight and strength have continued to increase. Glycosuria has been found in traces on five days, chiefly in connection with an attack of influenza. Otherwise, the urine is reported clear but hyperglycemia is the rule. Further increases of dosage will doubtless become necessary if the present diet and its attendant rise of weight are to be continued.

Case No. 1255. (Mild juvenile diabetes. Use of insulin for improving nutrition and for prophylaxis.) Male. American. Age 14 years. Height 5 feet 7¼ inches. Weight 120 lb. maximum, 117½ lb. at admission, October 13, 1922. Family and personal history were unimportant. Diabetes probably began in 1919, as indicated by slight languor and asthenia since that time. Nocturia in 1920 led to the diagnosis. The diet since has been strict though liberal. Glycosuria has tended to return occasionally, and last March there was a large boil on one cheek. The condition has become harder to control in the past three months and the entire loss of weight has occurred in that time.

The plasma sugar came to normal with one week of low diet, and the limit of tolerance was reached only with 70 gm. protein, 40 gm. carbohydrate, and 1600 calories, at a weight of 108 lb. This result would formerly have been considered very satisfactory; but beginning Nov. 18, 2 units of insulin was given, and the dosage and diet were increased in parallel until at discharge on Dec. 15, 1922, the patient was taking 70 gm. protein, 40 gm. carbohydrate and 2500 calories, with 6 units of insulin divided in two injections per day. This program has since been continued successfully at home. A few trivial hypoglycemic symptoms have been noticed, but there has been no glycosuria and no blood sugar report above 0.15 per cent.

The advantages of a case treated in a mild stage are here evident, for a liberal diet is made possible by relatively small insulin doses, which involve little danger of wide fluctations in the blood sugar. There should be a much better chance for normal development with 2500 than with 1600 calories, and the insulin is used not only for this purpose, but

also in the hope of providing an additional safeguard against further downward progress.

Case No. 1274. (Severe diabetes. Insulin requirement for protein and carbohydrate. Restoration of usefulness by insulin.) Male. American. Age 38 years. Height 5 feet 6¼ inches. Weight 155 lb. maximum, 108 lb. at admission, Nov. 13, 1922. The patient has been the only thin member of an obese family, in which no other case of diabetes has been known. The personal history was negative. He had been under continuous but lax treatment, with constant glycosuria.

There were no coma symptoms at admission, and the heavy glycosuria and acetonuria diminished with three days of semi-starvation. As the case was judged to be severe, insulin treatment was begun Nov. 16. The detailed record is given in paper No. 2 (Table 9). The requirement of 6 units of insulin daily to control the sugar in blood and urine on a diet of only 40 gm. protein and 10 gm. carbohydrate up to Dec. 2 confirmed the estimate of the severity of the case. Various foods were added successively in order to learn the insulin requirement. The treatment was not fully complete when the patient was discharged on Jan. 17, 1923. Glycosuria was present, and the previous diet was changed to 60 gm. protein, 35 gm. carbohydrate and 1500 calories. Glycosuria was present at first on 9 units of insulin and later with increases to 12 and 15 units per day, but has apparently been brought under control by 21 units with the same diet. The weight has increased to 117 lb., and the patient has returned to his work as a salesman. The greater part of the time his diet is unweighed but he has learned to estimate it accurately and thus keeps himself continuously free from glycosuria.

Case No. 1276. (Severe diabetes in well nourished juvenile patient. Insulin requirement for carbohydrate and protein.) Female. American. Age 14 years. Height 5 feet 3¾ inches. Weight 124 lb. maximum, 110 lb. at admission, Nov. 23, 1922. Family history—obesity and diabetes on paternal side. Personal history negative except for simple childhood infections. She has been obese but very vigorous and active. Loss of weight, thirst and polyuria in the summer of 1921 led to the finding of glycosuria. She was treated by carefully restricted diet to keep glycosuria absent. In the past summer, she had two gluteal abscesses, and glycosuria has not been successfully restrained since then.

At admission, heavy glycosuria and moderate ketonuria were present, with hyperglycemia of 0.395 per cent., but the child appeared so strong and well nourished that the case was estimated as mild. On a diet limited to 30 gm. protein, the urine cleared by Dec. 1, but the plasma sugar was still 0.300 per cent. Insulin was therefore begun in dosage of 1 unit on Dec. 3. The detailed record is given in paper No. 2 (Table 15). The severity of the case is indicated by the fact that continuance of very low diet to the end of December with 4 units of insulin daily failed to reduce the plasma sugar below 0.184 per cent. The patient was discharged Feb. 20, 1923, at a weight of 105 lb., on 80 gm. protein, 50 gm. carbohydrate and 1800 calories, with 15 units of insulin divided in three injections per

day. She has since remained free from glycosuria and other symptoms on this program at home, while the weight has increased to 111 lb. The diet will be so regulated as to prevent obesity.

Case No. 1277. (Severe diabetes, and chronic bronchitis. Abandonment of treatment after improvement.) Male. German Jew. Age 45 years. Height 5 feet 6 inches. Weight 150 lb. maximum one year ago, 90 lb. at admission, Nov. 26, 1922. Family history negative. Personal history negative except for bronchitis and asthma for years. He was accepted for life insurance seven years ago, and diabetes was diagnosed at onset of acute symptoms four years ago. He has had no treatment except in a hospital five months ago, and he abandoned diet immediately upon discharge.

At admission, the patient was extremely weak and emaciated, with heavy glycosuria and ketonuria but no coma symptoms. He had signs of bronchitis, cough and muco-purulent sputum, but was afebrile and not tuberculous as far as examinations could determine. The plasma sugar was 0.375 per cent. On a diet of only 30 gm. protein, the urine became clear on Dec. 7, but the plasma sugar was still 0.326 per cent. Insulin was then begun in dosage of 2 units daily, and the diet was increased to 35 gm. protein, 5 gm. carbohydrate, and 600 calories, with the result that the plasma sugar fell gradually to 0.173 per cent. on Dec. 18. By Dec. 24 the diet had been increased to 50 gm. protein, 10 gm. carbohydrate and 1200 calories, and the insulin to 4 units daily. On this program, glycosuria was absent and the last plasma sugar analysis was 0.189 per cent. The weight was still 90 lb., but the strength and general condition were obviously improved. On this date the patient was discharged at his own insistence, and he has not called for insulin or been heard from since.

The problem in this case was one which must be frequently encountered by hospitals. This was a charity patient whose mental attitude and record for fidelity were of the poorest, but the fact remains that he was nearly a dying man and such persons are regularly given the benefit of all the resources of medicine. The psychic effect of a wonderful new discovery and the obvious improvement accomplished may sometimes produce reform even in the most ignorant and careless. As soon as this patient felt sufficiently improved, he considered himself safe in going home and discarding all restraints, and ignored the opportunity to receive free insulin. In the future he will probably be treated similarly in some other hospital, but it is doubtful if the ultimate mortality among persons of this type can be reduced by insulin.*

Case No. 1283. (Diabetes with tuberculosis. Death.) Male. American. Age 48 years. Height 6 feet ¼ inch. Weight 225 lb. maximum eight years ago, 160 lb. at admission, Dec. 4, 1922. Family and personal history entirely negative. Steady loss of weight during the past eight years has been the only symptom. One month before admission, polyuria and cough caused the patient to consult a physician, who diagnosed

* Inquiry concerning this patient revealed the fact that he died on March 23, without making any attempt to follow the prescribed diet.

diabetes and probable tuberculosis. Sputum examinations in the Institute were continously negative until shortly before discharge, when abundant bacilli were found.

The intractable character of the diabetes gave further evidence of infection. On a diet of 30 gm. protein daily to Dec. 11, glycosuria fell to traces but the existing acidosis seriously increased. The diet was therefore changed to 30 gm. protein and 60 gm. carbohydrate from Dec. 12 to 15, and 30 gm. protein and 20 gm. carbohydrate from Dec. 16 to 23. Ketonuria thus cleared up but glycosuria slightly increased. With a return to 30 gm. protein and 5 gm. carbohydrate, the urine became entirely clear in two days but the plasma sugar on Dec. 26 was still 0.306 per cent. Continuance of the same diet to Jan. 6 reduced the hyperglycemia only to 0.203 per cent. The same diet with 2 units of insulin daily reduced the plasma sugar only to 0.184 per cent. by Jan. 14. The diet and dosage were then gradually increased, until by Jan. 30 the patient was taking 50 gm. protein, 70 gm. carbohydrate and 1320 calories, with 8 units of insulin per day. Glycosuria was absent but the plasma sugar was almost constant at 0.270 per cent. February 4 to 24, insulin was omitted altogether. On the same diet up to Feb. 10, glycosuria remained absent and the plasma sugar actually fell slightly to 0.242 per cent. The explanation of the seeming lack of influence of insulin is unknown. It also appears improbable that the patient had a true tolerance for 70 gm. carbohydrate, but the full explanation of the apparent rise of tolerance in some tuberculosis cases is not clear. Increase of the diet with fat to first 2500 and then 3500 calories led to the outbreak of glycosuria on Feb. 21. February 25, the use of insulin was resumed, and glycosuria ceased with the use of 12 units daily. An exact adjustment of dosage to diet was not established, because the patient's appetite became small and variable, and he commonly did not eat more than 2000 calories per day.

He was discharged March 5, weighing 122 lb., and distinctly weaker than at admission. It was hoped that. as hunger is one of the occasional symptoms of hypoglycemia, insulin might serve to stimulate appetite as well as provide for assimilation, so that increase of weight and strength might favor resistance to the infection. At home, however, it was difficult to induce the patient to take sufficient food, though the use of insulin permitted practically any choice to tempt a sick man. He was barely able to take 1700 calories, and though sugar did not appear in the urine, he grew progressively weaker and died March 26. In this case the tuberculosis was probably hopeless, even had there been no diabetes.

Case No. 1285. (Death from phlebitis and septicemia.) Male. German-American. Age 59 years. Height 5 feet 10 inches. Weight 175 lb. maximum, 160 lb. at admission, Dec. 5, 1922. The family history was negative, and the personal history negative except for typhoid at the age of 37. For the past 10 years the patient has known that he has had sugar in the urine, but has paid no attention to it. He has eaten sugar, starches, and everything else without restraint, and has used considerable alcohol and smoked excessively. He has felt well and has not suffered from any of the usual symptoms or complications.

In the past 2 months he has lost 15 lb. in weight, and has noticed increased thirst and capricious appetite. His physician prescribed a restricted diet, which he followed poorly, and glycosuria of 1 per cent. to 4.5 per cent. continued. Ten days ago the left thigh became swollen and intensely painful. Within 24 hours a tender mass the size of a hen's egg developed on the midpart of the anterior surface. The skin was only slightly inflamed. It was necessary for him to go to bed on account of the pain, which was aggravated by walking or moving the limb. Pain and edema of the left thigh and leg have increased progressively. Two days ago he became short of breath and drowsy. Blood cultures showed streptococci. He was admitted to the Institute on account of sepsis and impending coma.

The patient was an elderly adult male in acute distress, with deep and labored breathing and marked acetone odor. When sufficiently roused and urged, he answered questions clearly and relevantly, but within a few seconds the eyes would close and he would lapse into sleep. Examination was negative except for an elongated mass 3 by 6 inches over the anterior surface of the left thigh. No fluctuation or pulsation could be detected in it. The whole leg was swollen and edematous. The glands were swollen and tender. Right leg was normal. Blood pressure 145/82; pulse 108; respiration 22, temperature 98.4° F. White blood count 40,000, polymorphonuclears 97 per cent.

The patient was given a fat-poor diet of 30 gm. protein and 40 gm. carbohydrate, changed on the following day to 20 gm. protein and 60 gm. carbohydrate. He was given 10 to 20 gm. of sodium bicarbonate by mouth each day. Within 72 hours his condition had improved appreciably. He was able to sit up, and was less drowsy and dyspneic. On account of the scarcity of insulin, it was withheld until Dec. 8, when very small doses of 2 units twice daily were given. There was very little change in the condition of the left limb. Surgical measures were considered inadvisable since there was no evidence of pus formation. The temperature per rectum ranged from 96 to 98.4° F. Several white blood counts showed marked leukocytosis about 40,000.

December 9 the condition became critical. At 7 A. M. he was drowsy, and could be roused only with difficulty. He mumbled incoherently. There were several involuntary bladder and bowel movements. Dyspnea and hypernea increased markedly. Insulin treatment to the limit of the available supply was begun at 10 A. M., when 20 units were given subcutaneously, followed by 10 units at 11 A. M., 12 noon and 2 P. M., and 14 units at 7 P. M. A total of 184 gm. of carbohydrate in the form of orange juice, levulose and glucose was given from 8 A. M. to 8 P. M. The first 40 gm. of carbohydrate was given in the form of orange juice by mouth, but after 12 noon it was given as glucose or levulose intravenously. 5 gm. of sodium bicarbonate was given every three hours. The patient showed no improvement. The state of coma gradually became more profound. He was completely unconscious at 5 P. M., and died at 11 P. M.

The administration of insulin produced a considerable fall in plasma sugar concentration and a marked rise in plasma bicarbonate, as shown

TABLE 9

Case No. 1285

Date 1 2 99	Hour	Diet			Urine		Blood Plasma		Sodium Bicarbonate Gm.	Insulin, Units	Remarks
		P. Gm.	F. Gm.	C.H. Gm.	Glucose	Nitroprusside	Sugar Mg. Per 100 cc.	CO_2 Cap. Vol. %			
Dec. 5	.....	30	3	40	++++	++++	624	17	20	0	W. B. C. 40,000, vomiting. Leg painful and tender. Temperature 98.4.
6	.....	20	2	60	++++	++++	682	....	15	0	Drowsy and hyperneic. Temperature 98.6.
7	.....	20	3	60	++++	++++	577	19.5	10	0	Leg swollen, painful, tender. Temperature 96.
8	.....	20	3	60	++++	++++	682	14.7	20	4	Blood urea 36 mg. per 100 cc. Temperature 97.
9	8 a.m.	..	..	20	++++	++++	714	19.5	..	..	W. B. C. 40,000. Temperature 96.4. Drowsy.
	10	..	..	..	.....	.....	...	....	..	20	
	11	..	..	20	.....	.....	714	14.5	5	10	Lapsing into coma.
	12 noon	..	..	..	.....	.....	750	25.2	..	10	
	1 p.m.	..	..	24*	.....	.....	653	28.1	..	..	Temperature 97.1.
	2	..	..	..	.....	.....	...	29	5	10	
	3	..	..	40*	.....	.....	540	35.7	..	..	
	4	..	..	20*	.....	.....	430	43.0	..	..	
	5	..	..	..	.....	.....	566	....	5	..	
	6	..	..	20*	.....	.....	...	....	..	..	Progressively worse.
	7	..	..	20*	.....	.....	...	....	5	14	
	8	..	..	20*	.....	.....	...	....	..	..	
	10	..	..	..	.....	.....	...	....	..	..	
	11	..	..	..	.....	.....	600	....	..	..	Died.

*Intravenously.

by Table 9. At 8 A. M., before extract was administered, the plasma sugar was 714 mg. per 100 cc., while at 4 P. M., after the administration of 54 units. it had fallen to 430 mg. per 100 cc., and the plasma CO_2 capacity increased from 19.5 to 43.0 vol. per cent.

With the sepsis present, high leukocytosis and absence of fever, it seems improbable that anything more effective could have been done even if sufficient insulin had been available from the time of admission.

Case No. 1286. (Very severe diabetes. Insulin requirement with different diets. Great clinical benefit.) Male. American. Age 52 years. Height 5 feet 11 inches. Weight 200 lb. maximum eleven years ago, 143 lb. at admission, December 6, 1922. Family history negative. Personal history negative except for tonsillitis up to operation one year ago, and sinus infection five years ago. Diabetes was discovered in routine examination in 1912. Glycosuria has been controlled part of the time by diet, but there were mild acidosis symptoms in 1921, and during recent months all attempts to check sugar and acetone have failed. At admission, the patient appeared well except for slight weakness. He had heavy glycosuria, slight ketonuria, and plasma sugar of 0.385 per cent. On a diet of 30 gm. protein and 5 gm. carbohydrate, he continued to excrete appreciable quantities of sugar up to Dec. 16, and the plasma sugar was still 0.349 per cent. With 2 units of insulin daily on the same diet from Dec. 17 to 21, the glycosuria was only slightly diminished and the plasma sugar was 0.366 per cent. An increase of insulin to 4 units on Dec. 22 and 23 reduced the glycosuria to traces, but the plasma sugar was 0.341 per cent. After increase of the dosage to 6 units on Dec. 24, glycosuria ceased within 48 hours. With continuance of the same semi-starvation diet of 30 gm. protein and 5 gm. carbohydrate with 6 units of insulin daily, the plasma sugar by Jan. 6 had fallen only to 0.234 per cent. An increase of carbohydrate, making the diet 30 gm. protein and 20 gm. carbohydrate with the same insulin dosage, produced no effect upon the plasma sugar during the following week. During the next week, Jan. 14-21, fat was added to make a diet of 30 gm. protein, 20 gm. carbohydrate, and 900 calories (still an undernutrition ration) without appreciable change in the plasma sugar during this time. The weight by this time had fallen to its minimum of 127 lb., and the patient was decidedly thinner and weaker than at admission.

Increased supplies of insulin then permitted an increase of dosage and diet. For the assimilation of 50 gm. protein, 50 gm. carbohydrate, and 2000 calories, 15 units of insulin was found to suffice during two weeks. Glycosuria remained absent and hyperglycemia fell from 0.341 to 0.254 per cent. An increase to 80 gm. protein, 100 gm. carbohydrate, and 2500 calories caused glycosuria, which required 27 units of insulin per day for its control.

The patient was discharged on this program Jan. 21, 1923, weighing 136 lb. By the middle of March his weight had increased to 150 lb., and the same diet was still balanced by the same dosage of insulin, without glycosuria. A slight recovery of tolerance by the patient is thus perhaps indicated.

The case was one of exceptional severity, as proved by the extraordinary difficulty in achieving sugar freedom with the combination of prolonged semi-starvation and insulin. It is doubtful whether glycosuria could have been stopped by undernutrition alone, and scarcely possible that life could have been saved on any diet for any long time either with or without glycosuria. Dextrose-nitrogen ratios were not obtained, but if it can be assumed that the pancreatic islands of the patient were almost completely out of function, some theoretical deductions may be made concerning the amounts of insulin necessary for the assimilation of certain diets. The remarkable practical result is that such a patient could be sent back to his business in practically normal health.

Case No. 1295. (Early stage of juvenile diabetes. Use of insulin for nutrition and prophylaxis. Female. Irish American. Age 6 years. Height 3 feet 10¾ inches. Weight 40 lb. maximum, 37 lb. at admission, Dec. 15, 1922. Family all healthy, long lived and thin; no diabetes. Personal history clear, except for whooping cough in infancy. Five weeks before admission, she went to bed with an ordinary cold and temperature not above 101° F. With it, thirst and polyuria began acutely and heavy glycosuria was discovered.

On admission, the child appeared well though somewhat frail. The glycosuria and slight ketonuria cleared up after two days of a diet of 40 gm. protein and 30 gm. carbohydrate. Increases of diet brought indications that the tolerance was not far from 800 calories, and insulin was begun Jan. 18, 1923, for the sake of more liberal nutrition. The patient was discharged Feb. 2, 1923, on 50 gm. protein, 75 gm. carbohydrate, and 1015 calories, with 4 units of insulin divided in two injections daily. The plasma sugar was slightly above normal. The weight was 38 lb.

At home, the diet has gradually been increased to 60 gm. protein, 65 gm. carbohydrate, and 1500 calories, and the insulin to 13 units daily. The weight has increased to 41 lb. and the general condition is very good. Traces of glycosuria still appear occasionally, so that further adjustments are required.

Case No. 1296. (Juvenile diabetes. Coma treated unsuccessfully with insulin.) Male. American. Age 13 years. Height and maximum weight not known. Weight 80 lb. at admission, Dec. 16, 1922 (11.45 P. M.). With the exception of diabetes in a maternal grandfather, the family history is negative. The patient was always thin, but well except for mild childhood disorders. Four weeks ago he complained of cloudy vision, and was unable to see letters on the blackboard at school. His mother noticed that for a week past he had urinated frequently during the day and three and four times during the night. He was excessively thirsty and ate ravenously, while he lost 2 pounds of weight in one week. The family physician diagnosed diabetes, and prescribed a diet of meat, fish, eggs, vegetables, cream, butter and olive oil. There was no improvement symptomatically. During the second week following diagnosis he lost 6 lb. in weight. Four days ago he became violently ill, with vomiting, drowsiness and dyspnea. 48 hours ago he became weaker and slept

TABLE 10

Case No. 1296

Date 1922	Hour	C.H. Gm.	Blood Plasma			Sodium Bicarbonate Gm.	Insulin, Units	Remarks
			Sugar Mg. Per 100 cc.	CO_2 Cap. Vol. %	Nitroprusside			
Dec. 16	11.45 p.m.	15	1876	13.7	++++	..	20	Insulin given intravenously. Vomiting.
17	12.30 a.m.	..	2000	....	+++	..	10	Vomited. Respirations 36. Comatose.
	1.00	25	....	....	.....	5	15	Swallows with difficulty.
	4.50	10	....	....	.....	..	20	Progressively worse. Respirations 30. Pulse 100.
	8.30	..	1500	29 0	+++	..	..	Vomited.
	9.00	10	....	....	.....	10	10	Pulse irregular, weak.
	10.30	..	1304	48 1	+	..	..	Respirations 28. Pulse 130.
	11.00	20	....	....	.....	5	15	
	11.45	5	....	....	.....	..	..	
	12.30 p.m.	10	938	57 6	+	5	..	Slightly better. Easier to rouse.
	2.00	..	....	....	.....	..	20	Vomits frequently. Pulse 160. Respirations 32.
	3.00		....	....	.....	..	20	Condition worse. Unconscious. Pulse weak, irregular.
	3.30	..	625	71 5	0	..	..	Unable to take fluids by mouth.
	4.00	..	....	....	.....	..	20	Pulse weaker. Condition critical.
	5.00	..	....	....	.....	..	20	1000 cc. saline subcutaneously.
	6.00	..	469	67.2	0	..	20	Pulse 148. Respirations 36.
	7.00	5	....	....	.....	..	..	
	10.00	..	....	....	.....	..	..	Patient died. Urine sugar 3.39%.

almost continuously. When awake he complained of thirst and drank large quantities of water, but refused or vomited food. Sixteen hours before admission he became comatose; he recognized no one and could not be roused, and was barely able to swallow fluids placed in his mouth. The physical examination was negative except for the usual picture of coma. Table 10 shows the treatment and chemical findings.

The plasma sugar of 2 per cent. (carefully verified) is the highest in our experience and probably the highest on record. It will be noticed that there was a continuous fall in the hyperglycemia, the originally heavy acetone reaction of the plasma disappeared completely, and the CO_2 capacity rose to high normal levels. For about 8 hours there seemed to be some clinical improvement, but not to the extent of recovery of consciousness. When fluids could no longer be given by mouth, hypodermoclysis with a liter of saline solution produced no effect. Weakness and unconsciousness progressed to death at 10 P. M.

Case No. 1302. (Juvenile diabetes. Death in coma with insufficient insulin dosage.) Female. American. Age 11 years. Height and weight not known. Admitted Jan. 2, 1923. Parents are living and well. No history of diabetes in the family. Always a sickly child; never strong. At the age of 16 months she had very severe pneumonia which lasted for eight weeks. Four years ago she suffered from cramps in the abdomen, which came on suddenly and lasted for 48 hours. Physician diagnosed appendicitis, but she has never been operated upon. During the attack there was no jaundice, diarrhea or fatty stools. She had another such attack two years ago. Diet was always normal, and she ate heartily, but her mother always considered her undernourished.

Six weeks ago the parents noticed that the child was unusually thirsty and passed large quantities of urine frequently. Bed-wetting, which was unusual for her, began about that time. These symptoms have persisted up to the present. She was never fond of sweets, but during the past six weeks has craved candy, desserts and starches, and her appetite has been ravenous. A week ago a small furuncle appeared on the left buttock, which opened spontaneously and drained for a few days. Ten days ago her parents noticed that she was losing weight, and they are certain that she has lost 5 lb. in the past five days. Symptoms of acidosis developed yesterday. She was drowsy and listless, and vomited several times early yesterday morning. She was nauseated the whole of the morning, and her mother gave her only hot milk. Severe vomiting began and has continued up to the present time. She complained of headache, and drank enormous quantities of water. A physician was called at 8 o'clock last night, who immediately diagnosed diabetes and acidosis. He prescribed abundant fluids and soda by mouth, and after four hours milk and liberal carbohydrates. Today she continued drowsy and has grown progressively weaker.

The patient, a poorly nourished, weak girl of about 11, was admitted to the Institute in a semi-comatose condition and vomited immediately on admission. Respirations were deep and stertorous, especially when

TABLE 11

Case No. 1302

Date 1923	Hour	C.H. Gm.	Blood Plasma			Sodium Bicarbonate Gm.	Insulin, Units	Remarks
			Sugar Mg. Per 100 cc.	CO_2 Cap. Vol. %	Nitroprusside			
Jan. 2	3.00 a.m.	10	....	....	.....	5	..	Admitted. Given water; vomited immediately.
	3.20	..	885	....	++++	..	..	Vomiting frequently. Drowsy.
	3.55	24	....	....	.....	..	..	Weak. Hyperpneic. Becoming drowsier.
	4.05	..	....	....	.....	5	23	
	4.35	10	....	....	.....	..	..	Vomited.
	5.00	..	....	....	.....	..	10	Breathing suppressed, shallow. Sleeping constantly.
	5.15	..	770	....	++++	..	..	Vomited.
	5.20	15	....	....	.....	..	..	
	5.50	10	....	....	.....	..	..	Urine: acetone and FeCl$_3$ heavy; 5.3% sugar; acetone, .204%.
	6.30	..	....	....	.....	..	..	Can barely be roused.
	7.00	..	....	....	.....	..	10	
	7.45	..	750	....	++++	..	25	
	8.10	..	....	....	.....	..	..	Patient died.

she was roused for any length of time. Heavy odor of acetone on the breath. General examination negative.

The usual methods of treatment of acidosis were begun immediately following admission at 3 A. M., namely, carbohydrate by mouth, forced fluids, enemata, purgatives, and small quantities of sodium bicarbonate by mouth. After she had taken fluids she vomited, and seemed to improve slightly for about 45 minutes. She voluntarily sat up in bed, and later seemed to sleep normally, but afterward she gradually became stuporous and the breathing more stertorous. During the first hour 34 gm. of carbohydrate was given by mouth, but insulin was withheld because the supply on this particular day happened to be short and the patient seemed able to recover without it. With the change for the worse, however, 23 units was administered, followed at 5 A. M. by 10 more units. Later experience has proved that such small dosage in severe acidosis and coma is entirely inadequate. About one hour after the second dose of insulin, breathing was quieter and the patient could be roused sufficiently to give her name and address, but later sank deeper into coma. 10 units of extract was administered at 7 A. M. and 25 units at 7:45 A. M. A trivial fall of plasma sugar was the only result, as shown in Table 11. She died at 8:10 A. M. This case is one which could probably have been saved had sufficient insulin been available.

Case No. 1303. (Severe juvenile diabetes. Insulin requirement for carbohydrate.) Male. American. Age 6 years. Height 4 feet 1 inch. Weight 48 lb. maximum, 40 lb. at admission, January 4, 1923. Family history—diabetes on paternal side. Personal history entirely clear except for double pneumonia four years ago. Enuresis and weakness 9 months ago led to diagnosis of diabetes. Attempts to control sugar have been unsuccessful.

At admission, heavy glycosuria and ketonuria were present without signs of coma. The plasma sugar was 0.334 per cent. After a diet of only 25 gm. protein and 5 gm. carbohydrate to Jan. 16, acetone nearly disappeared, slight glycosuria was still present, and the plasma sugar had risen to 0.375 per cent. Addition of fat to make first 800 and then 1600 calories without change in the protein and carbohydrate increased the 24 hour sugar output from traces to 2.9 gm. within three days. Omission of fat and giving of 4 units of insulin cleared the urine within 24 hours.

The detailed record is given in paper No .2 (Table 4). At discharge on Feb. 14, 1923, the boy was taking 60 gm. protein, 75 gm. carbohydrate, and 1000 calories, with 8 units of insulin divided in two injections per day. Glycosuria was absent but hyperglycemia present. At home, glycosuria appeared within a few days, and the insulin was increased to 12 units and the diet changed to 60 gm. protein, 50 gm. carbohydrate, and 1300 calories. No more than traces of glycosuria now appear, but the adjustment of diet and dosage is not completed. The weight has increased to 48 lb. and there has been a corresponding gain of strength. Though the previous tolerance was not accurately determined, it is evident that the case was very severe and that insulin has tremendously improved assimilation and nutrition.

Case No. 1304. (Severe diabetes. Insulin requirement for reduction of hyperglycemia. Influence of fat.) Male. Jewish-American. Age 32 years. Height 5 feet 6 inches. Weight 128 lb. maximum, 104 lb. at admission, Jan. 6, 1923. Family and personal history entirely negative. Patient denies ever having had any illness. He has been thin and strong, following mixed occupations as a clerk and a prize-fighter. In July, 1921, glycosuria was discovered through recent onset of weakness, thirst and loss of weight. Dietary restriction has been very slight and he has progressed downward with continuous glycosuria.

At admission, glycosuria and ketonuria were heavy and the plasma sugar was 0.395 per cent. On a diet of only 30 gm. protein, the condition proved to be remarkably intractable. 20 gm. or more of glucose was excreted daily up to Jan. 22; the quantity then fell off rapidly and the urine was clear on Jan. 26, though the plasma sugar was still 0.263 per cent. Owing to invisible water retention, the weight fell only to 98 lb. The patient was perceptibly but not seriously weakened. The same low

TABLE 12

Case No. 1304

Date 1923	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Feb.								
2	30	62	5	700	0	242	99	2
3	"	"	"	"	0	...	...	2
4	"	"	"	"	0	...	98	2
5	"	"	"	"	0	171	...	2
6	"	"	"	"	0	...	99	2
7	"	"	"	"	0	175	...	2
8	40	4	5	216	0	169	101	2
9	40	5	5	225	0	154	..	2
10	40	0	5	180	0	152	102	2
11	"	"	"	"	0	...	..	2
12	"	"	"	"	0	...	103	2
13	"	"	"	"	0	150	..	2
14	"	"	"	"	0	126	99	2
15	"	"	"	"	0	142	..	2
16	40	80	5	900	0	121	97	2
17	"	"	"	"	0	...	..	2
18	"	"	"	"	0	...	100	2
19	"	"	"	"	0	143	..	2
20	"	"	"	"	0	...	99	2
21	"	"	"	"	0	192	..	2

diet was continued to Feb. 1 in the attempt to reduce the blood sugar, which on the following morning was 0.242 per cent. Insulin treatment was therefore begun Feb. 2, 1923, in dosage of 2 units daily.

The table shows a part of this patient's record illustrating two points.

First, glycosuria had been absent for the preceding week, but the reduction of the blood sugar to normal required 2 units of insulin per day in addition to the prolonged undernutrition up to Feb. 16. The difference between hyperglycemia and normal plasma sugar in this case was therefore at least 2 units of insulin. Second, with the diet of 30 gm. protein, 5 gm. carbohydrate and 700 calories the plasma sugar fell only to 0.175 per cent. by Feb. 7. But with an increase of protein to 40 gm. and exclusion of fat, the normal plasma sugar of 0.121 per cent. was reached on the morning of Feb. 16. Then, with the addition of 80 gm. of fat to raise the total calories to 900 per day, the plasma sugar rose to 0.192 per cent. on Feb. 21, illustrating the greater burden placed upon the pancreatic function by a Newburgh type of diet as compared with the undernutrition method.

The diet was then rapidly built up, so that at discharge on March 11, 1923. the patient was taking 80 gm. protein, 80 gm. carbohydrate and 2500 calories. His weight was 99 pounds. Glycosuria was present, which the dosage of 16 units of insulin was probably inadequate to control, but a need for further adjustments of diet and dosage was anticipated under any circumstances. The reason for this expectation is that the insulin dosage required to date appears unduly small for such a diet in a case of such apparent severity. This discrepancy is probably explainable by the existing state of emaciation. As the body weight rises with this diet, it is expected that the insulin requirement will increase considerably unless the patient's own tolerance increases beyond anticipation.

Case. No. 1305. (Severe diabetes. Insulin requirement for protein, carbohydrate and fat. Unusual gain in tolerance.) Male. American. Age 39 years. Height 5 feet 6 inches. Weight 198 lb. maximum in 1918, 118 lb. at admission, Jan. 7, 1923. Family history—two relatives on the paternal side are diabetic. The patient declares that he has always been well, except for having spent seven weeks in bed with a severe attack of influenza in 1918. Later in that year he had sciatica. The urine is said to have been normal in a routine examination in the summer of 1920. Polyuria and weakness in the fall of 1921 led to the diagnosis of diabetes. The weight at that time, however. was 171 lb., in consequence of a steady decline since 1918. The diets employed have not arrested the glycosuria or the general downward progress.

At admission, glycosuria was heavy and ketonuria slight. The plasma sugar was 0.336 per cent. On a diet of only 35 gm. protein and 5 gm. carbohydrate, the patient still excreted 36 gm. glucose on Jan. 17 and 28 gm. on Jan. 18. Insulin treatment was then begun, owing to the evident severity of the case. With dosage of 4 units daily, the sugar excretion was reduced to 14.7 gm. on Jan. 19 and to small quantities on the following days, and ceased Jan. 23.

The detailed record is given in paper No. 2 (Table 13). Insulin was omitted from Feb. 21 to March 19, and the omission for a time at least seemed to leave the tolerance practically unchanged. Thus, up to Feb. 27 a diet of 200 gm. protein, 80 gm. carbohydrate and 1480 calories was apparently tolerated, and up to March 11 a diet of 100 gm. protein, 138

gm. carbohydrate and 1480 calories caused only occasional traces of glycosuria. An increase of fat to make 100 gm. protein, 128 gm. carbohydrate and 2172 calories resulted in heavier glycosuria and required resumption of insulin. The weight remained very slightly changed. Such a gain of tolerance, especially for protein and carbohydrate, has been foreign to our previous experience with any cases of this severity. The impression is therefore created that insulin brought about a considerable improvement of pancreatic function in this case. Upon discharge March 31, he was free from glycosuria on the above diet with 10 units of insulin, 5 units before breakfast and 5 before supper. He still remains free from glycosuria, and a blood sugar analysis taken during digestion of the noon meal on April 21 was 0.075 per cent. The weight was 120 lb., and he was able to do regular work.

Case No. 1306. (Incipient juvenile diabetes. Use of insulin for improved nutrition and for prophylaxis and attempt at cure.) Male. Jewish-American. Age 9 years. Height 4 feet 4 inches. Weight 62 lb. three months ago, 52 lb. at admission, Jan. 7, 1923. The family are obese, and one brother of the patient died of diabetes at the age of 20. The patient has always been well except for measles and one attack of tonsillitis. He has lost 10 lb. in the last three months, and the onset of thirst and polyuria seven weeks before admission led to the discovery of heavy glycosuria. This ceased with slight dietary restriction, and the condition has appeared so mild as to create doubt of the diagnosis.

At admission, both urine and blood were normal, and a diet of 70 gm. protein, 55 gm. carbohydrate and 2000 calories was tolerated without hyperglycemia either fasting or during digestion. A test with 50 gm. of glucose before breakfast, however, resulted in heavy glycosuria and unusually high plasma sugars of 0.555 per cent. at one hour and 0.341 per cent. at two hours. The boy was discharged Feb. 4 at a weight of 57 lb., with normal plasma sugar on the diet mentioned.

He was readmitted March 1, still apparently normal. The giving of 2 units of insulin per day caused no hypoglycemia, and the dose was increased to 4 units daily and the diet to 80 gm. protein, 100 gm. carbohydrate and 2400 calories. The weight rose to 61 lb., and an increase of insulin to 10 units per day (5 units before breakfast and 5 units before supper) gradually became necessary. The patient was discharged on this program on April 19, free from hyperglycemia at all times of the day.

In this very early but genuine juvenile diabetes, insulin was used with a double purpose; first, to allow a diet with ample carbohydrate and calories to provide for growth and development; second, as a prophylactic to guard against downward progress and to aid in effecting a cure if such a thing is possible. The question will be whether the growing pancreas of a young child can produce new islands or repair the old ones to a sufficient extent for cure of the diabetes, when the damage has been comparatively slight and when the insular function is spared to the greatest possible extent.

Case No. 1307. (Severe diabetes. Insulin treatment conducted chiefly

at home.) Male. American. Age 45 years. Height 6 feet. Weight 175 lb. maximum, 135 lb. at admission, Jan. 8, 1923. Family and personal history negative. Loss of weight and strength began 2½ years ago, and diabetes was diagnosed a few months later. The diet prescribed was unlimited in protein and fat and the patient also was careless, so that glycosuria has continued.

A diet of 35 gm. protein and 5 gm. carbohydrate up to Jan. 15 failed to clear the urine. Insulin was therefore begun in dosage of 2 units per day, and glycosuria ceased on the same diet within two days, though hyperglycemia continued. January 21, the diet was increased to 50 gm. protein, 10 gm. carbohydrate and 800 calories, and the insulin to 8 units daily. On the following day it became necessary for him to return to his home for business reasons. The home management was therefore entrusted to a nurse trained in both diet and insulin treatment. Gradual increases have since been made to 60 gm. protein, 30 gm. carbohydrate, 1500 calories and 21 units of insulin per day. The patient is free from glycosuria and the blood reports from a local laboratory are nearly normal. He continues to gain slightly in weight and strength, but the progress has been much slower than would have been possible under institutional conditions.

Case No. 1308. (Moderate diabetes. Influence of distribution of insulin doses.) Male. American. Age 41 years. Height 6 feet. Weight 170 lb. maximum five years ago, 106 lb. at admission, January 8, 1923. The family and personal history were negative. He may have been losing weight for several years, but diabetes was diagnosed only with the onset of marked thirst and weakness in March, 1922. As a war veteran, he was treated in a U. S. hospital until October 20, 1922. Here his symptoms were controlled by reduced diet, and he subsequently remained in good condition at home except for emaciation and weakness. He was then referred to this Institute largely in order to receive insulin. The plasma sugar was normal at admission. A diet of 70 gm. protein, 40 gm. carbohydrate and 1900 calories apparently represented the upper limit of tolerance, as judged by the slight hyperglycemia which resulted. An increase to 80 gm. protein, 50 gm. carbohydrate and 2500 calories caused a sharp rise of blood sugar immediately and glycosuria within five days. Insulin treatment was begun Feb. 22. Dosage of 10 units daily abolished glycosuria but not hyperglycemia up to March 3, but with rise of weight to 110 lb. marked glycosuria occurred on the same program.

The experiment was then tried of giving all the insulin for each day in one dose just before supper. The diet by March 25 was built up to 100 gm. protein, 100 gm. carbohydrate and 3000 calories, the entire additional food being given at the evening meal. Increase of insulin dosage to 30 units per day, given all at once as mentioned, caused no hypoglycemic symptoms but failed to prevent heavy continuous glycosuria. Beginning April 8, a change was made by giving the insulin in the form of three doses of 10 units each, one before each meal. The record for a few days preceding and following this change is given in Table 13, to show the radical change resulting.

The patient is still in the Institute. His weight has risen to 120 lb.,

and it has become necessary to increase the insulin to 36 units (12 units three times a day) in order to stop glycosuria. As the plasma sugar is still high and the weight increasing, further increases of dosage or reduction of diet will undoubtedly become necessary before a permanent result is attained.

TABLE 13

Case No. 1308

Date 1923	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
April								
5	100	241	100	3000	32.3	385	113	30
6	"	"	"	"	38.0	...	...	30
7	"	"	"	"	60.0	375 540*	114	30
8	"	"	"	"	0	...	...	30
9	"	"	"	"	14.9	...	116	30
10	"	"	"	"	8.6	...	...	30
11	"	"	"	"	4.9	...	115	30
12	"	"	"	"	3.9	405	...	30
13	"	"	"	"	4.8	...	116	30
14	"	"	"	"	9.9	...	...	30

*Blood sample taken at 5 p.m., before supper or insulin.
Other blood samples taken before breakfast.

Case No. 1312. (Mild diabetes. Benefit to neurotic state through improved nutrition with insulin.) Female. American. Age 55 years. Height 5 feet 1 inch. Weight 165 lb. maximum, 129 lb. at admission, Jan. 13, 1923. Family history unimportant. Personal history—Owing to attacks of jaundice and pain over gallbladder, an operation was performed 10 years ago in which an inflamed gallbladder containing no stones is said to have been removed. Diabetes was discovered at about the same time. The blood pressure has been elevated for some years, 170-180 systolic, 80-100 diastolic. Her chief symptoms are increasing weakness, nervousness and loss of weight. Glycosuria has been nearly continuous on haphazard diets.

The glycosuria ceased within two days on 45 gm. protein, 10 gm. carbohydrate and 800 calories, and a tolerance for 55 gm. protein, 40 gm. carbohydrate and 1400 calories was established within a week. Insulin was then begun in dosage of 2 units per day, and the diet and dosage were gradually increased. The patient was discharged April 7, 1923, after having tolerated for several weeks a diet of 80 gm. protein, 100 gm. carbohydrate and 2200 calories, with 14 units of insulin divided in two injections per day, at a weight of 126 lb. To allow for greater activity at

home, the diet has since been increased to 2500 calories and the insulin to 16 units.

The condition here was a rather mild diabetes, with a possible tolerance for 1800 or 2000 calories with low carbohydrate. She is well-meaning and well situated, but her poor mentality and highly neurotic nature are partly a result of diabetes and arteriosclerosis and partly a cause of further downward progress. The blood pressure has been brought to normal by the usual chloride restriction, and insulin has permitted assimilation of a diet which is both satisfying and strengthening. The condition heretofore has been made worse by too much confinement, because the patient positively refused to make any exertion when feeling weak. With increased strength she can now be urged to exercise, and both her muscles and nerves seem to be improved. The actual prognosis without insulin would have been probable death after a few years of invalidism, no matter how feasible dietary control of the diabetes might be theoretically. A dietitian will be needed for the management of the treatment at home, and with such care it seems possible for the patient both to live and to enjoy life.

Case No. 1316. (Severe senile diabetes. Infection of foot. Insulin used to raise tolerance. Carbohydrate experiment.) Male. German. Age 64 years. Height 5 feet 3 inches. Weight 162 lb. maximum, 115 lb. at admission, January 18, 1923. Family and personal history negative. Diabetes was discovered in 1916, after his weight had fallen from 162 lb. to 117 lb. in nine years. About a month before admission he trimmed off some calloused skin under the ball of his right foot, and an ulcer developed which has continued to discharge pus and shown no tendency to heal.

On a diet of 40 gm. protein and 5 gm. carbohydrate, glycosuria ceased in five days and the plasma sugar in four more days was reduced to 0.199 per cent. A diet of 50 gm. protein, 10 gm. carbohydrate and 800 calories for a week then resulted in hyperglycemia of 0.234 per cent, and a trace of glycosuria. As the case was evidently severe, insulin treatment was begun on Feb. 4 to avoid further undernutrition. The detailed record is given in paper No. 2 (Table 1). The infection in the foot began to heal well under the diet treatment and the healing was completed at about the same rate under insulin. The diet was built up to 65 gm. protein, 50 gm. carbohydrate and 1800 calories, with which the patient was discharged March 15, 1923, sugar-free on 15 units of insulin divided in two injections per day, at a weight of 113 lb. The benefit of the insulin consists in the higher diet and strength as compared with what would have been possible with diet alone.

Case No. 1317. (Very severe diabetes. Successful use of insulin for coma. Insulin requirement for carbohydrate. Improvement in nutrition and fidelity.) Female. American. Age 47 years. Height 5 feet 3 inches. Weight 140 lb. maximum, 90 lb. at admission, Jan. 19, 1923. The family history is clear except for obesity and nephritis in the father. Mumps and tonsillitis in adult life have been her only known infections. Diabetes

was diagnosed July 1, 1920, after it had apparently been present six months. She underwent thorough hospital treatment. She could be kept free from symptoms only on a diet of approximately 1000 calories at a weight of 110 lb. She was reasonably faithful for nearly a year, then became more and more careless, and for the past year has eaten with very little restraint. Glycosuria and acidosis have been heavy and increasing, until acute signs of coma developed in the night and she was rushed by ambulance to the Institute in the early morning hours.

Dyspnea was marked but unconsciousness not complete. Injections of 25 units of insulin intravenously and 25 units subcutaneously were immediately given. During the ensuing 24 hours the patient received a total of 50 gm. glucose, 100 cc. lemon juice, 500 cc. orange juice, 15 gm. sodium bicarbonate, and abundance of water. Some of the laboratory findings at this time are given with the rest of the record in paper No. 2 (Table 5). From 13.7 vol. per cent., the plasma bicarbonate had risen by the following morning to 50.0 vol. per cent., acetone had disappeared from the urine and blood plasma, and the patient seemed entirely out of danger. The attempt was made to give a low diet without insulin on January 20, with a view to learning the tolerance. By the morning of January 21 the patient was again almost in coma, with plasma bicarbonate of 30.9 vol. per cent. In divided doses of 20 to 30 units, a total of 160 units of insulin had to be given through the day to avert the danger. As shown in the table mentioned, the plasma bicarbonate in absence of bicarbonate dosage remained subnormal for several days. At first, 30 units of insulin daily was inadequate to prevent glycosuria on a diet of 500 calories, but by January 30 when acidosis had cleared up, this dosage proved adequate. The diet was built up as shown in paper No. 2, and the patient was discharged March 8 on 80 gm. protein, 120 gm. carbohydrate, 2789 calories and 50 units of insulin.

After returning home glycosuria persisted in both morning and evening specimens for two weeks, then the evening tests showed negative results. Insulin was reduced to 40 units on April 1 and to 34 units on April 11. The morning tests since that time have shown traces of sugar while tests later in the day are clear, and hypoglycemic reaction have occurred occasionally about 8 P. M. Body weight on April 15 was 124 lb. After weight and strength are further improved, it may be advisable to reduce the present diet in order to keep all symptoms smoothly under control.

Judged by the history and observations, the diabetes was of extreme severity, possibly "total," and obviously hopeless for any living diet if it had proved possible to control it by diet at all. Insulin was thus life-saving in two respects, first by saving from acidosis, the fatal character of which was proved by the prompt return of coma symptoms when insulin was withdrawn, and second by making possible a diet which was sufficient not only to support life but also to command the patient's fidelity.

Case No. 1319. (Severe infantile diabetes. Improved nutrition and prognosis.) Female. American. Age 15 months. Height 2 feet 9½ inches. Weight 27 lb. maximum, 20 lb. at admission, Jan. 28, 1923. Fam-

ily and personal history are entirely negative. The baby had no known illness until about Jan. 1 nervousness, thirst, polyuria and loss of weight and strength began to be noticed. A physician who was called Jan. 26 referred the patient to this Institute because of heavy glycosuria and acidosis.

At admission, the plasma sugar was 0.500 per cent. and all the usual signs of impending coma were present. It was judged that these were not so extreme but that ordinary treatment would suffice, and the acute danger actually passed off without the use of insulin. A diet of 20 gm. protein and 15 gm. carbohydrate, strictly fat-free, from Feb. 1 to 3 reduced the sugar and acetone to traces. With 2 units of insulin daily, the urine immediately became clear but the plasma sugar on Feb. 7 was still 0.171 per cent. The diet and dosage were then gradually increased, until at discharge March 10, 1923, the patient was receiving 50 gm. protein, 50 gm. carbohydrate and 900 calories, with 12 units of insulin divided in three injections per day. Both urine and blood were strictly normal, and the weight had risen to 25 lb. The clinical improvement was very evident. It is well known that such a case at such an age has heretofore been controllable only by radical undernutrition and the tendency to downward progress has always been very strong. Insulin has already restored the child to nearly normal nutrition, and the future of such a patient will furnish a strict test of the possibility of preventing downward progress by means of insulin.

Case No. 1321. (Diabetic coma, with fatal result in spite of high insulin dosage. Autopsy.) Female. Hebrew. Age 28 years. Height 5 feet 5 inches. Weight 139 lb. maximum, 102 lb. at admission, Feb. 2, 1923. The family history was clear of any known diabetes, obesity or other hereditary disease. The patient had no illnesses in early life except attacks of tonsillitis, which ceased after tonsillectomy three years ago. She was married three years ago. Shortly afterward, psoriasis appeared on one foot and then spread gradually to other parts of body, resisting all treatment. She has never been pregnant. One year ago she had whooping cough, otherwise has been entirely well. She has always had a normal figure, with no tendency to obesity, and has committed no excesses In food or other habits.

On account of psoriasis, she was kept for nearly a year on almost exclusively cereal diet, until slight loss of welght was noticed and an examination of the urine showed sugar. This disappeared with moderate restrictions of carbohydrate, and for two years she has felt herself entirely well, though glycosuria has been present and she has gradually lost further weight. She was in excellent strength and spirits until the morning of February 1, when she vomited after a hearty breakfast and complained of a severe pain in the back of the neck. Two doses of aspirin were given, in the belief that she had contracted the prevalent influenza. Further vomiting occurred, dyspnea developed and consciousness became impaired. She could still recognize people in the forenoon of February 2, but when admitted to the Institute had been completely unconscious for several hours. The rectal temperature was 99.5 degrees, the pulse 100 to

140, of fair quality, and the respiration 24 to 48 per minute, of typical air-hunger type. The record of treatment in the Institute is shown in Table 14.

The several liters of water given by mouth are not recorded, because of the inaccuracy introduced by vomiting. The first 20-unit dose of insulin recorded was given intravenously; all of the others were given subcutaneously.

It will be noticed that the plasma sugar at admission was very high, namely 882 mg. per 100 cc. and the plasma bicarbonate was unusually low, namely 10.9 volumes per cent. Within less than 20 hours (viz. from 5 P. M. February 2 to noon February 3) a total of 370 units of insulin was given. This was spaced out fairly uniformly in doses of 20 to 30 units, while abundant carbohydrate was given by mouth and also intravenously to prevent hypoglycemia and provide material for the burning of acetone bodies. The maximum effect from the chemical standpoint was observed between this time and 5:20 P. M. It will be noticed that at 2:25 P. M. a specimen of urine was obtained which was free from both sugar and acetone. At 3:30 and 5:20 P. M. the plasma sugar reached a low point of 0.23 per cent., while the plasma bicarbonate reached a high point of 44 to 46 volumes per cent. At this time the clinical condition appeared hopeless. It had grown worse in proportion as the chemical tests had become better. The patient was profoundly unconscious, unable to swallow, dangerously weak and almost pulseless at the wrist. The fear was entertained that there might be such a thing as collapse from the large insulin dosage notwithstanding the continuous hyperglycemia. Saline solution, glucose and levulose were injected intravenously as shown, so that by 8 P. M. the plasma sugar was elevated to 0.536 per cent. Insulin was completely withdrawn, except for a small precautionary dose of 5 units at 1 A. M. February 4. During these night hours without insulin the chemical findings grew worse while the clinical condition very greatly improved. By 7.15 A. M. on February 4 the plasma sugar was 1.5 per cent., and the CO_2 capacity had fallen to 29 volumes per cent. Meanwhile, the power of swallowing had first returned, and consciousness was gradually restored, so that at the time of the test at 7:15 A. M. the patient was able to recognize persons and to answer questions feebly but intelligently. She was practically free from dyspnea, had a strong and regular pulse at the wrist, took skim milk and orange juice with relish, and seemed on the road to recovery. By 8 A. M. the condition had changed rapidly. The markedly increasing dyspnea and failing consciousness showed a return of typical diabetic coma, so that there was no choice but to resume insulin treatment, at first in small doses, and increasing as these proved ineffective. Notwithstanding insulin, bicarbonate and saline injections, which slightly lowered the plasma sugar and raised the CO_2 capacity to 50 volumes per cent., the coma progressed in typical manner to a fatal end at 3:40 P. M. February 4.

No explanation can be offered for the clinical peculiarities. It is practically out of the question that a patient received in such deep coma would have recovered consciousness without the aid of insulin. This

TABLE 14

Case No. 1321

Hour	Blood Plasma					Urine				Insulin, Units	Other Treatment and Remarks
	Sugar Mg. per 100 cc.	NaCl Mg. per 100 cc.	Urea Mg. per 100 cc.	Acetone Mg. per 100 cc.	CO_2 Cap. Vol. %	Vol. cc.	Sugar %	Nitroprusside	Ferric Chloride		
Feb. 2											
5.00 p.m.	....	....	....	..	....	...	....	....	....	..	Admitted in coma.
5.20	882	515	44	89	10.9	...	....	....	....	20	Intravenous injection.
5.25	....	....	....	..	....	...	....	....	....	50	Subcutaneous injection.
5.30	....	....	....	..	....	...	....	....	....	..	200 cc. orange juice.
5.45	....	....	....	..	....	...	....	....	....	..	5 gm. sodium bicarbonate.
6.00	....	....	....	..	....	...	....	....	....	25	
6.30	....	....	....	..	....	...	....	....	....	..	200 cc. orange juice.
6.45	1000	....	....	79	19.5	...	....	....	....	30	
7.15	....	....	....	..	....	...	....	....	....	..	200 cc. water
7.50	....	....	....	..	....	...	....	....	....	..	Dyspnea much relieved.
8.15	....	....	....	..	....	...	....	....	....	20	Conscious at times.
8.30	....	....	....	..	....	...	....	....	....	..	120 cc. orange juice.
9.10	....	....	....	..	....	...	....	....	....	25	
10.40	810	564	38	81	29.0	...	....	....	....	20	Vomited.
11.00	....	....	....	..	....	....	....	....	....	..	150 cc. orange juice.
11.30	....	....	....	..	....	760	2.62	++++	+	..	
Feb. 3											
12.15 a.m.	....	....	....	..	....	...	....	....	....	..	20 gm. glucose and 100 cc. orange juice. Vomited immediately.
12.20	....	....	....	..	....	...	....	....	....	20	
1.20	....	....	....	..	....	...	....	....	....	20	
2.30	....	....	....	..	....	...	....	....	....	20	
2.40	....	....	....	..	....	....	....	....	....	..	150 cc. orange juice.
3.20	612	548	58	..	38.5	70	2.22	+++	0	..	150 cc. orange juice.
4.30	....	....	....	..	....	...	....	....	....	20	Conscious for 10 minutes.
4.45	....	....	....	..	....	...	....	....	....	..	200 cc. orange juice.

6.30	....	....	....	..	....	5	....	+	0	20	200 cc. orange juice.
7.30	500	562	80	92	47.1	...	....	....	....	..	
8.30	....	....	....	..	....	...	....	....	....	20	Vomited.
9.10	400	....	....	..	36.5	...	....	....	....	..	500 cc. saline solution.
9.20	....	....	....	..	....	...	....	....	....	30	
11.45	....	....	....	..	....	...	....	....	....	30	
12.30 p.m.	280	....	....	68	40.4	...	....	....	....	..	25 gm. glucose in 500 cc. normal saline.
2.25	....	....	....	..	....	30	0	0	0	..	
3.30	232	....	....	..	44.3	...	....	....	....	..	
5.20	236	....	....	..	46.2	...	....	....	....	..	600 cc. saline, 25 gm. glucose, 20 gm. levulose, injected intravenously.
5.45	....	....	....	..	....	...	....	....	....	..	75 cc. orange juice.
8.00	536	548	61	55	37.6	...	....	....	....	..	500 cc. saline solution, 25 gm. glucose, 10 gm. levulose.
10.30	....	....	....	..	....	...	....	....	....	..	30 cc. milk by tube.
11.10	....	....	....	..	....	...	....	....	....	..	60 cc. orange juice.
12 m.	....	....	....	..	....	...	....	....	....	..	90 cc. milk by tube.
Feb. 4											
1.00 a.m.	....	....	....	..	....	...	....	....	....	5	
1.20	....	....	....	..	....	...	....	....	....	..	45 cc. orange juice.
2.45	....	....	....	..	....	...	....	....	....	..	30 cc. orange juice.
4.00	....	....	....	..	....	...	....	....	....	..	100 cc. milk.
6.00	....	....	....	..	....	55	1.77	....	....	..	Sudden collapse. 30 cc. orange juice.
7.15	1500	513	94	6	29.0	...	....	....	....	..	
7.30	....	....	....	..	....	...	....	....	....	5	Cup hot broth. 25 gm. egg albumin.
8.00	....	....	....	..	....	...	....	....	....	10	
9.30	....	....	....	..	....	...	....	....	....	..	30 cc. milk.
10.00	....	....	....	..	....	...	....	....	....	10	50 cc. milk.
10.30	1500	....	....	7	31.9	...	....	....	....	25	
11.45	....	....	....	..	....	...	....	....	....	..	
12.30 p.m.	....	....	....	..	....	...	....	....	....	10	250 cc. saline. 5 gm. soda.
12.45	1304	....	....	..	37.6	...	....	....	....	50	
1.45	....	....	....	..	....	...	....	....	....	..	
2.00	....	....	....	..	....	...	....	....	....	..	500 cc. saline, 5 gm. soda bicarbonate
2.15	1154	..	....	..	41.3	...	....	....	....	25	
2.45	....	....	....	..	....	...	....	....	....	..	
3.35	910	529	128	44	50.0	...	....	....	....	..	
3.40	....	....	....	..	....	...	....	....	....	..	Died.

opinion is confirmed by the fact that when insulin was omitted for about 20 hours, a return of typical diabetic coma occurred. The dosage of insulin in the first place had been very large, but it had been given in a series of medium sized injections with close watching of its effects, and the clinical progress had been steadily downward. If the insulin was responsible in any unknown way for the increasing weakness, the later results show at least that the conditions would also have been fatal without insulin.

Permission was obtained for an immediate autopsy, to the extent of a small abdominal incision to obtain specimens of the principal viscera. The liver, kidneys and spleen were normal to gross examination, and the gallbladder was free from inflammation or stones as far as could be determined without opening it. First, portions of liver were cut up into boiling water without delaying to obtain scales for weighing. Small specimens of liver and of abdominal muscle were next taken in alcohol for glycogen stains. The pancreas was next removed entire; it was not weighed, but appeared normal in size, color and consistency. The only noteworthy feature was a sprinkling of a few small fat necroses in the adipose tissue immediately in contact with the pancreas and nowhere else in the peritoneum. The head, body and tail of the pancreas were cut up separately as usual into Zenker and formaldehyde solutions. Microscopic specimens were then taken in these solutions from the liver, kidneys and spleen. The intestine was everywhere distended with gas; near the stomach it contained a moderate amount of fluid, but was nearly empty below. In examining it, a coil was found, about two feet long, in the upper ileum several feet from the jejunum, which was a deep dusky red, in contrast to the normal color of the rest of the bowel. In delivering it, a pin-point area of ulceration or necrosis gave way, permitting an escape of gas. There were no adhesions, and no appearances like peritonitis either clinically or postmortem. No strangulation, obstruction or other cause for the condition could be found. Microscopic specimens were taken from this part of the bowel.

Glycogen.

Glycogen was not demonstrated micrscopically in the muscle, but was very plentiful in the liver sections stained with Best's carmine.

A sample of liver tissue, after boiling in water, weighed 20 gm. After hydrolysis with KOH and the usual chemical procedures, the glycogen in this was found to be 2.07 gm., or 10.35 per cent. If it be assumed that this liver sample weighed as much as 30 gm. when fresh, its glycogen content would still be 6.9 per cent. There is, therefore, no doubt that the liver of the human diabetic is enabled by insulin to store large quantities of glycogen, as was proved for the livers of diabetic dogs by Banting, Best, Collip, Macleod and Noble.[1] It is still more noteworthy that this power is manifested in a coma patient, that such high percentages of glycogen are maintained through the long agonal period, and that death occurs in spite of such glycogen formation. It is unfortunate that the apparent absence of glycogen in the muscles was not verified by chemical examination.

Microscopic Pathology.

In the ulcerated area of the intestine, the mucosa was absent and generally also the submucosa. On the naked surface of the muscular coat were dense masses of bacteria, mostly large bacilli, and colonies of these were found also occasionally between the muscle bundles. From the absence of any inflammatory reaction or leukoctyes, the process was judged to be merely an agonal necrosis and not connected with the pancreatic lesions.

The liver was strictly normal, without inflammation, degeneration, or even congestion or fatty infiltration. Fat was represented only by small vacuoles in all the cells, such as are found even in glycogen-rich livers. There were no differences between center and periphery of the lobules.

The spleen was somewhat congested and its Malpighian bodies were prominent.

The kidneys were free from structural abnormalities. The glomerular capsules and most of the tubules were moderately distended and showed slight albuminous precipitates in the lumina. A few tubules contained casts. No Armanni vacuolation was discoverable in the Henle tubules. This statement is not fully conclusive because it is based on examination of routine stains of Zenker fixed material, and no glycogen or fat stains were made. As there was glycosuria most of the time and hyperglycemia all the time, the reason for such a rapid and complete disappearance of vacuolation is uncertain.

The pancreas was completely free from fibrosis, in the form either of scars in the parenchyma or the familiar slight thickening along the island capillaries. The lesions present were acute, and affected chiefly the body of the organ. They consisted of interstitial leukocytic infiltrations in occasional areas, where the interlobular septa were broadened by edema and invaded by small or large masses of cells, among which Mallory's endothelial leukocytes were greatly outnumbered by polymorphonuclears. In the body of the gland these accumulations were often large enough to be called purulent. In the head and tail they were smaller and fewer, but yet every section from the entire pancreas showed some such infiltrations. Less prominent were occasional small hemorrhages. The changes were strictly acute, fibroblasts and organization being absent, and also strictly localized, the great mass of the parenchyma showing no injury or reaction whatever.

The acini were irregular in size and shape, but mostly contained little zymogen. In searching sections somewhat less than 1 sq. cm. in area and 4 micra thick, the number of islands was found greatly reduced. They were most numerous by far in the body, where 44 sections averaged 6 islands per section. Only 17 islands could be found in 57 sections from the head, and only 2 in 80 sections from the tail. The identification of islands in the head and tail was also sometimes uncertain, for the small groups consisting of only a few cells might perhaps sometimes be duct proliferations instead of true islands. The islands in the body were of normal size and structure. A striking feature was the comparative ab-

sence of hydropic degeneration. Altogether 3 islands (2 in the body, 1 in the head) were found showing distinct vacuolation of a few cells. This degree of the change is unusually slight for a coma case. As there were no signs of fibrous or hyalin replacement, the possibility is suggested that the numerical reduction of islands was due to previous hydropic degeneration, and if so the rarity of this change at autopsy would be still more remarkable.

Case No. 1331. (Severe diabetes with pulmonary tuberculosis and empyema. Improved nutrition.) Male. American. Age 21 years. Height 5 feet 7½ inches. Weight 120 lb. maximum, 92 lb. at admission, Feb. 20, 1923. Family history negative. Personal history—measles in childhood, later scarlet fever followed by double otitis media, and permanent partial deafness. At 12 years, he had an abscess in the right axilla which slowly disappeared spontaneously. Adenoids and tonsils were removed at 13. Diabetes was diagnosed promptly with the onset of typical symptoms 1½ years ago. Under treatment of a chiropractor without diet restriction, the downward progress was rapid. Two weeks before admission he entered a hospital and is said to have become sugar-free after

TABLE 15

Case No. 1331

Date 1923	Diet				Plasma Sugar Mg. per 100 cc.	Urine			Insulin, Units	Body Weight Lb.
	P. Gm.	F. Gm.	C.H. Gm.	Total Cal.		Vol. cc.	Glucose	Nitroprusside		
Feb.										
20	20	6	0	134	...	....	.....	.....	..	.....
21	30	8	0	192	429	800	.....	.....	..	92½
22	30	10	0	210	...	....	++++	++	..	.....
23	30	6	0	174	...	1550	++++	++	..	92
24	30	10	0	210	209	1200	++++	.....	..	.....
25	60	73	25	1000	...	3300	++++	++	6	.....
26	"	"	"	"	341	2300	++++	++	6	.....
27	"	"	"	"	...	....	++++	+	6	92
28	"	"	"	"	...	3400	++++	.....	12	.....
Mar.										
1	"	"	"	"	...	3000	.....	.....	12	92
2	"	"	"	"	349	3600	++	++	12	.....
3	"	"	"	"	...	1300	+++	.....	12	105
4	70	117	40	1500	...	3300	0	+++	16	.....
5	"	"	"	"	...	2000	0	++	16	111
6	"	"	"	"	...	3400	+	+	16	.....
7	"	"	"	"	272	2900	0	+	16	102
8	100	144	75	2000	...	3500	0	+	16	.....
9	"	"	"	"	...	2600	++	0	16	92
10	"	"	"	"	334	3300	++	+	16	.....
11	"	"	"	"	...	4500	+	0	20	94
12	"	"	"	"	...	3300	0	0	20	.....
13	"	"	"	"	...	2900	0	0	20	.....
14	"	"	"	"	...	2700	0	0	20	.....
15	"	"	"	"	...	....	0	0	20	.....

three days of fasting, but following his discharge he has had glycosuria, cough, and pleurisy with fever.

At admission, the temperature was normal, but the physical signs were those of bronchitis, probably tuberculosis, especially in the left lung, and a small effusion in the left pleura. With a syringe and needle, 30 cc. of thick gray pus was withdrawn from this pleura, and the signs of effusion then diminished. No tubercle bacilli were found in the sputum. On a diet limited to 30 gm. protein, the urine still contained 26.6 gm. of sugar on Feb. 24. The next day the diet was increased to 60 gm. protein, 25 gm. carbohydrate and 1000 calories, and 6 units of insulin given. The glycosuria was 43.6 gm. on this day, 33.1 gm. on Feb. 26, and the analysis on Feb. 27 was incomplete. With the same diet and an increase of insulin to 12 units, marked glycosuria continued to March 3, but ceased with an increased dosage of 16 units on March 4. Increases were then made rapidly, so that the patient was discharged March 20, 1923, on 100 gm. protein, 75 gm. carbohydrate and 2000 calories. Glycosuria was thus absent or faint. On March 11 the dosage was raised to 20 units per day. His condition improved markedly, and the cough and expectoration became much less. The sputum has remained negative for tubercle bacilli. The pain in the chest disappeared. A third puncture failed to reveal pus. He is growing stronger and more active.

The prognosis for the infection would be doubtful even without diabetes. With diabetes of this severity, diet treatment would have been practically ineffectual and death would almost certainly have occurred within three months. The higher nutrition made possible by insulin will certainly extend life considerably beyond this period if the treatment is carried out with reasonable efficiency. The environment of the patient is poor, and it has therefore been necessary to allow him to show glycosuria frequently, rather than incur the dangers of either undernutrition or hypoglycemia in such a case. It is to be feared that the hyperglycemia and occasional glycosuria may lower the resistance to the infection, but this is a question which awaits an answer from longer experience with insulin treatment. The results to date are better than could well have been anticipated in a case of this character.

Case No. 1332. (Moderate diabetes. Liberal diet with insulin. Influence of fat.) Male. Jewish-American. Age 28 years. Height 5 feet 7¼ inches. Weight 127 lb. maximum, 108 lb. at admission, Feb. 21, 1923. Family and personal history negative. He had one boil in November, 1921, and polyphagia and polydipsia developing in January, 1922, led to the diagnosis of diabetes. He has been treated at home and in army hospitals but has progressed downward seriously. At admission, there was moderate glycosuria and hyperglycemia of 0.300 per cent., but no acidosis. A diet of 30 gm. protein and 5 gm. carbohydrate cleared the urine in three days.

With a diet of 60 gm. protein, 30 gm. carbohydrate and 18 to 33 gm. fat from Feb. 25 to March 6, 8 units of insulin daily sufficed to prevent glycosuria and to cause a gradual reduction of plasma sugar from 0.254 to 0.156 per cent. Leaving the protein and carbohydrate unchanged, in-

crease of fat to make first 1500 and then 2000 calories resulted in a gradual rise of the plasma sugar to 0.206 per cent. and the beginning of glycosuria on Feb. 17, with the same dosage of 8 units of insulin.

Both diet and dosage were then increased, so that at discharge on March 30 he was receiving 100 gm. protein, 80 gm. carbohydrate, 2300 calories and 33 units of insulin per day.

Case No. 1333. (Juvenile diabetes. Use of insulin for improved nutrition and prophylaxis.) Male. American. Age 3 years. Height 3 feet 4¾ inches. Weight 40 lb. maximum, 39 lb. at admission, Feb. 22, 1923. Family and personal history negative. In the midst of perfect health, enuresis began August 29, 1922, and the family physician immediately discovered glycosuria. Moderate dietary restriction has since kept glycosuria absent, and both blood and urine were normal at admission.

Conditions continued normal until the diet was gradually increased to 60 gm. protein, 60 gm. carbohydrate and 1200 calories, when moderate glycosuria began. The use of insulin was begun, and the diet and dosage increased to 80 gm. protein, 100 gm. carbohydrate, 1500 calories and 12 units of insulin per day. The weight has risen to 41 lb. The urine is thus kept normal and the plasma sugar nearly so, but the dosage will be increased to maintain as low a plasma sugar level as may be feasible within normal limits. There is the usual double purpose in the use of insulin for an early juvenile case; first, for raising the nutritive level so as to favor growth and development; second, for prophylaxis against downward progress and for favoring a cure if any possible chance exists for the boy to outgrow the condition.

Case No. 1334. (Moderate diabetes. Improvement of neurosis with insulin.) Female. American. Age 47 years. Height 5 feet 3 inches. Weight 208 lb. maximum eight years ago, 131 lb. at admission, Feb. 22, 1923. The family are obese, and one sister died of diabetes. The patient boasts never to have been ill even to the extent of a sore throat or headache. Diabetes was diagnosed in October, 1920, on the appearance of polyphagia and polyuria, but has probably been present for at least eight years as judged by the loss of weight. The diet at first was inefficient and coma was barely escaped in April, 1921, but careful treatment since that time kept the condition under control until the patient began to estimate food instead of weighing it, and glycosuria gradually returned.

At admission, glycosuria of 51 gm. and hyperglycemia of 0.341 per cent. were present, without acidosis. With two days of a diet of 50 gm. protein and 30 gm. carbohydrate, the sugar excretion fell to 12.3 gm., indicating that the condition could be controlled fairly easily. With continuance of the same diet and 4 units of insulin daily, the urinary sugar fell to 3.65 gm., 2.52 gm., and 0 on successive days. With the same diet and 8 units of insulin daily, the plasma sugar by March 3 had fallen only to 0.223 per cent. The diet and dosage were then rapidly built up until by March 21 they amounted to 80 gm. protein, 80 gm. carbohydrate, 2500 calories and 20 units of insulin divided in two injections per day. The patient was discharged April 1 on this program and has continued to

progress favorably. Glycosuria was absent, but further adjustments will be necessary to control hyperglycemia.

The diabetes in this case was by no means of extreme severity or uncontrollable by diet, but the special feature was the extremely neurotic character of the patient. Even with the best dietary control of the diabetes, she must still have been an invalid on account of her nerves. At present, she is by no means normal nervously, but the condition is greatly improved with the more liberal nutrition made possible by insulin. She can now be urged to use exercise and other invigorating measures, and there is reasonable hope of much greater improvement. Diet was rigidly adhered to and a report on April 19 stated that the urine, which was tested twice daily, was free of sugar.

Case No. 1335. (Moderate diabetes, with abscesses of limbs.) Female. Hebrew. Age 52 years. Height 5 feet 5½ inches. Weight 180 lb. maximum, 13 years ago. Admitted Feb. 23, 1923. No diabetes is known in the family. The patient has been married for 20 years; has five children living and well; all are obese. She has led an active healthy life without any serious illness.

Diabetes was diagnosed 11 years ago, within a week after onset of extreme thirst and polyuria. During the first three months of the disease she lost 35 lb. in weight, from 180 to 145 lb., and has kept about the latter weight since. A year after the onset she went to Carlsbad where she was treated for four weeks. The urine was free of sugar on a few occasions. After returning home she neglected diet entirely, and during the ensuing seven years did not attempt to follow any restrictions, except that she avoided sugar and ate pastry only occasionally. She felt very well, except for thirst, polyuria and pruritus vulvae. Two years ago she had acute amaurosis, which her oculist told her was due to diabetes, so she placed herself under the care of a physician and followed a careful diet, and the vision returned to normal. For the past year diet has been lax and glycosuria constant, though she has felt well.

On Feb. 5, 1923, the middle toe of the left foot became painful and red, and two days later it turned purple. She was put to bed and the foot elevated. The diet was better regulated and the toe was restored to normal within ten days. On Feb. 15 she noticed that her left thigh and both forearms were slightly stiff, and 24 hours later they were swollen and tender. The skin was tense and red, and the underlying tissues and muscles were hard and indurated. Swelling, pain, induration and tenderness increased until the thigh and forearms were twice as large as normal and were so painful that she could not sleep. Fluctuation could not be detected. Her temperature ranged from 100° to 101° F.

On Feb. 21 she awoke with headache and vomited on arising. She was also drowsy and dyspneic. Her physician gave her liberal carbohydrate, forced fluids and soda by mouth, and by evening she felt much better. The following morning, however, the symptoms returned and she slept the greater part of the time. By noon she was hyperpneic, sleepy and nauseated, and vomited several times.

TABLE 16—Case No. 1335

Date 1923	Hour	Diet			Urine				Blood Plasma					Sodium Bicarb. Gm.	Insulin, Units	Remarks
		P. Gm.	C.H. Gm.	Total Cal.	Vol. cc.	Glycosuria Gm.	Nitroprusside	$FeCl_3$	Sugar Mg. per 100 cc.	Blood Urea Mg. per 100 cc.	CO_2 Cap. Vol. %	Nitroprusside	Total Acetone Mg. per 100 cc.			
Feb.																
22	5.00 p.m.	..	40	....	420	12.7	++++	..	502	19	12.	++++	38.5	..	45	Drowsy.
	5.05	..	..	....	....	....	....	..	....	..	....	....	....	..	..	Gradually weaker and drowsier.
	5.35	..	....	....	....	....	....	..	....	..	....	....	....	....	15	
	5.40	..	....	....	....	....	....	..	....	..	....	....	....	5	..	Vomited immediately after soda.
	6.00	..	....	....	....	....	....	..	....	..	....	....	....	....	50	Rapidly becoming comatose; difficult to rouse.
	7.00	..	20	....	....	....	....	..	....	..	....	....	....	....	..	
	7.15	..	..	....	....	....	....	..	368	19	20.4	++++	....	....	..	Breathing better and not so hyperpneic.
	9.30	..	....	....	....	....	....	..	....	..	....	....	....	....	30	
	10.00	..	....	....	660	13.7	....	..	....	..	....	....	....	5	..	
	11.30	..	....	....	....	....	....	..	....	..	....	....	....	....	50	
23	2.00 a.m.	..	....	....	400	4.1	....	..	....	..	....	....	....	....	20	
	8.00	4	20	....	330	2.8	....	..	....	..	....	....	....	....	..	
	11.30	..	....	....	....	....	....	..	319	..	50	++	....	5	10	Improved but still drowsy. Pulse 98. Respiration 28.
	11.45	6	20	....	....	....	....	..	....	..	....	....	....	....	..	Arm painful. Nauseated.
	2.45 p.m.	4	15	....	....	....	....	..	....	..	....	....	....	....	10	
	5.30	3	3	....	....	....	....	..	....	..	....	....	....	....	..	
	6.30	..	....	....	....	....	....	..	....	..	....	....	....	....	10	
	7.00	..	10	....	....	....	....	..	....	..	....	....	....	....	..	Temp. 98. Pulse 92. Respiration 24.
	9.00	..	14	....	....	....	....	..	....	..	....	....	....	....	..	
	12.00 m.	..	10	....	800	8.6	+++	..	....	..	....	....	....	....	15	
24	8.00 a.m.	50	60	740	1400	+++	....	..	326	26	....	++	....	....	40	Insulin in doses of 10 units q. 6 h.
	5.00 p.m.	..	..	....	....	....	....	..	326	18	64.1	....	....	5	..	
25	8.00 a.m.	50	60	740	1800	18.0	....	..	268	20	71.	....	....	....	40	
	7.00 p.m.	..	..	....	....	....	....	..	306	..	....	....	....	....	..	
26	.....	50	60	740	....	3.22	....	..	263	18	....	....	....	....	40	
27	.....	"	"	"	2200	+	....	..	....	..	....	....	....	....	40	
28	.....	"	"	"	2200	+	....	..	164	..	....	....	....	....	40	
Mar.																
1	....	60	60	780	1800	....	....	..	283	..	....	....	....	....	40	
2	....	"	"	"	2200	0	....	..	....	..	....	....	....	....	40	
3	....	"	"	"	1700	0	....	..	206	18	65.3	....	....	....	40	
4	.....	"	"	"	1450	7.20	....	..	....	..	....	....	....	....	40	Drainage of abscesses of arms.
5	.....	"	"	"	2000	+	....	..	....	..	....	....	....	....	40	
6	.....	65	100	1800	1000	+	....	..	268	..	72.9	....	....	....	40	
7	.....	"	"	"	1750	....	....	..	....	..	....	....	....	....	40	
8	....	"	"	"	2500	40.76	....	..	....	..	....	....	....	....	30	
9	....	"	"	"	1700	35.70	....	..	....	..	....	....	....	....	30	
10	....	"	"	"	1650	9.74	....	..	....	..	....	....	....	....	30	
11	.....	"	"	"	2000	27.10	....	..	....	..	....	....	....	....	30	Operation; drainage of abscess of thigh.
12	.....	"	"	"	....	....	....	..	416	..	....	....	....	....	42	

She was seen in consultation at her home at 5 P. M. on Feb. 22. Examination showed the conditions mentioned. Treatment was begun in advance of examination by administration of 45 units of insulin. She was also given forced fluids and carbohydrate by mouth. Maximum insulin dosage was not used because the case seemed to be not of extreme severity. Table 16 shows the treatment and chemical findings. About 7 P. M. improvement became noticeable. Respirations were quieter and consciousness clearer. She was able to take water by mouth, but objected to glucose or orange juice; therefore, small portions of bread and jam were given. She rested well during the night and drank water and orange juice well.

The following morning she was transferred to the Institute. She was still drowsy and complained of extreme pain in the arms and leg, and was hardly able to flex them. She was given a diet of 17 gm. protein and 90 gm. carbohydrate, without fat. During the following 24 hours, 45 units of insulin were administered at 6-hour intervals. On Feb. 24 she was given a diet of 50 gm. protein, 60 gm. carbohydrate and 900 calories, with 10 units of insulin every six hours. Glycosuria persisted until Feb. 28. On March 1 the diet was increased to 60 gm. protein, 60 gm. carbohydrate and 1500 calories, with the same amount of insulin, and glycosuria remained absent.

Sleep had been disturbed considerably on account of the painful condition of the arms. Morphine had been administered each evening since admission. On March 4 definite fluctuation could be made out in the arms; with ethyl chloride anesthesia, both arms were incised and a large quantity of thick yellow material was expressed. Abundant drainage continued for three days, and healing took place in a rapid and normal manner. The abcess on the thigh was opened and drained under gas-ether anesthesia on March 12, and about 300 cc. of thick yellow pus was evacuated. The patient recovered quickly from the operation, and the wound is still open but healing well.

Case No. 1336. (Gangrene of both feet. Unsuccessful insulin treatment.) Male. American. Age 62 years. Height 6 feet 1½ inches. Weight 235 lb. maximum six years ago, about 180 lb. at admission, Feb. 25, 1923. The family history was irrelevant. Twenty years ago the patient was sick in bed for three weeks with lobar pneumonia. He has led a sedentary life of indoor work without exercise, but has always felt well.

The diagnosis of diabetes was made 2 years ago, following symptoms of weakness, fatigue, polyuria, thirst and loss of weight, which had been present for about five months. The weight dropped from 235 lb. to 192 lb. during that time. The symptoms cleared promptly with lax dietary prescriptions, though glycosuria continued.

January 18, 1923, he suddenly developed pain, tenderness and redness of the great toes and the two medial toes of both feet. The pain increased rapidly, and within a week the toes were purplish and a small gangrenous area about 2 cm. in diameter appeared on the plantar surface of the left foot, with a small amount of purulent discharge. On Feb. 1 the distal

portion of the right great toe became necrotic, and part of the distal phalanx was removed. The gangrene slowly advanced in both feet, and four days ago they were so painful that sleep was impossible. There has been an abundant purulent discharge with foul odor. Two days ago the whole of the left foot became swollen, red and tender, with radiating pain up the calf of the leg.

The general examination at admission was negative. The patient was somewhat weak, but calm and without complaint except for the pain in the feet. There was a necrotic area about 1½ cm. in diameter over the dorsum of the great toe of the right foot, with a sinus exposing necrotic bone. The adjoining skin was inflamed, tender and red. The dorsalis pedis artery was thicker than normal, but pulsated strongly.

The great toe and the 2nd and 3rd toes of the left foot were necrotic and partially mummified. The gangrenous area extended upward over the distal portion of the foot for about ½ inch, but there was no clear line of demarcation. The whole foot had an angry, red appearance, and was very painful and tender. The dorsalis pedis artery could not be palpated, but there was good pulsation in the popliteal space. The temporal, radial and brachial arteries were palpable but not especially thickened.

The patient was placed on a nearly fat free diet of 50 gm. protein and 50 gm. carbohydrate, with increasing doses of insulin to stop glycosuria and reduce hyperglycemia. During 6 days of this treatment, weakness gradually increased. Cellulitis of the left foot extended upward to the ankle, but by the third day after admission a definite line of demarcation could be made out. On March 2, six days after admission, the left leg was amputated below the knee, and the great toe and adjoining necrotic area of the right foot were removed, because it was feared that the strength was too low for a double amputation. The shock from the brief operation was unexpectedly great, and the patient was stuporous, perspiring and in danger of death for the several days following. Appetite was absent and vomiting was easily induced. The patient first consented to take whiskey and milk, and it was considered necessary to remove all dietary restrictions in order to tempt him to eat anything possible. He gradually became able to take fairly liberal quantities of various cereals, ice cream, custards, junket, etc. This diet was probably adequate, but it could not be accurately reckoned because of the character of the foods, refusal of portions and occasional vomiting. It was considered unsafe to push the insulin dosage to the point of abolishing glycosuria, for fear that hypoglycemia might occur unexpectedly in such a weakened state and prove fatal. Insulin was therefore regulated so as to keep glycosuria within fairly moderate bounds. The wounds showed no tendency whatever to heal. On the fifth day after the operation, about 200 cc. of pus was expressed from the amputation wound of the leg. All stitches were removed. A large sloughing area 2 inches in diameter appeared in the anterior skin flap, and finally sloughed entirely, leaving the muscles exposed about two inches, with the tibia and fibula protruding. Insulin was therefore increased by March 19 to 60 units per day, for the purpose of abolishing glycosuria and somewhat reducing hyperglycemia. The

TABLE 17

Case No. 1336

Date 1923	Urine			Blood Plasma				Insulin, Units	Remarks
	Vol. cc.	Nitro-prusside	Glycosuria Gm.	Sugar Mg. Per 100 cc.	NaCl Mg. Per 100 cc.	Blood Urea, Mg. Per 100 cc.	CO_2 Cap. Vol. %		
Feb.									
25	....	0	+++	306	577	36	57.6	10	Insulin in 2 doses of 5 units each.
26	....	+	++	....	....	....	....	10	Gangrenous processes extending rapidly.
27	....	+	++	212	....	....	....	15	
28	....	0	3.36	....	....	....	....	15	Gangrene of left foot demarcating.
Mar.									
1	1600	0	0	300	....	....	51.0	20	
2	1550	0	0	270	527	58	....	20	Amputation of left leg and 3 toes of right foot.
3	875	0	0	238	519	50	60.5	24	Perspiring profusely, listless, threatened collapse.
4	1300	0	0	270	....	....	64.3	16	No appetite. Weak. Whiskey and milk.
5	1500	0	2.60	270	503	76	....	16	No appetite. Weak. Whiskey and milk.
6	1300	+	7.35	220	....	....	76.0	8	No appetite. Weak. Whiskey and milk.
7	1500	0	16.28	469	441	58	....	8	White blood count 12,600.
8	1500	+	23.20	385	581	66	....	24	100 gm. levulose intravenously.
9	1900	++	19.30	....	....	....	....	24	Weak, perspiring. Insulin t. i. d.
10	1650	+	24.00	....	....	....	....	24	
11	1150	0	7.30	....	....	....	....	24	
12	500	0	31.63	....	....	....	....	32	Appetite slightly improved. Stronger.
13	1850	+	16.20	....	....	....	....	36	
14	1500	0	10.08	536	585	130	....	36	
15	1600	0	37.64	....	....	....	....	36	
16	1930	0	15.87	....	....	....	....	36	
17	1300	0	5.82	....	....	....	....	42	
18	1180	0	7.43	577	....	104	....	54	Insulin 4 times a day.
19	1410	0	0	....	....	....	....	60	
20	1140	0	0	....	....	....	....	60	
21	1220	0	0	....	....	....	....	60	
22	1020	0	0	....	....	....	....	60	
23	750	0	0	366	....	....	50.0	70	
24	....	0	0	....	....	....	....	....	
25	....	....	....	242	594	....	....	....	

muscles and skin then became somewhat dryer and discharged less pus, but there was still little attempt at granulation. The wound at the site of the amputation of the toe of the right foot was in equally bad condition, and an area of dry gangrene appeared on the heel of this foot notwithstanding avoidance of pressure. He slept the greater part of the time, and was listless and apathetic. He took practically no nourishment, except small quantities of ice cream and whiskey. In the closing days there was a septic temperature of 99° to 103° F. On March 24 pulse and breathing were weak, and death occurred at 5 o'clock the following morning.

Case No. 1344. (Moderately severe diabetes. Avoidance of undernutrition by insulin. Influence of protein addition.) Female. American. Age 40 years. Height 5 feet 3 inches. Weight 99 lb. maximum, 76 lb. at admission, March 4, 1923. Family history negative except for obesity in father. Personal history includes only measles in childhood and pneumonia at 22. Polydipsia in December, 1920, led to discovery of 5 per cent. glycosuria. Treatment has not prevented further glycosuria and emaciation.

On a diet of 50 gm. protein, 20 gm. carbohydrate and 1200 calories, the patient excreted 11 to 6 gm. of glucose daily for four days. 4 units of insulin then cleared the urine immediately. The brief record with insulin is given in paper No. 2 (Table 14). She has gained weight to 81 lb., and avoidance of the usual initial undernutrition is the only feature of the case to date. Since discharge from the Institute on April 1, she has remained free of glycosuria on 80 gm. protein, 80 gm. carbohydrate and 1800 calories and has been able to resume her duties as book-keeper. Her insulin dosage is 18 units daily.

Case No. 1346. (Juvenile diabetes. Successful treatment of coma with insulin.) Male. American. Age 10 years. Height 4 feet 10 inches. Weight 73 lb. maximum, 68 lb. at admission (with clothes), March 5, 1923. Father and mother living and well. No history of diabetes in the family. At birth the patient and his mother were jaundiced for ten days. He has been always strong and well, and has had only whooping cough; no tonsillitis or other illnesses.

Listlessness, drowsiness, polyuria and thirst were noticed only about five days prior to his admission on March 5. By March 4 sleepiness and dyspnea were marked, and he had pain and cramps in the epigastrium with tenderness on deep pressure. The appetite was lost completely and he was nauseated, but did not vomit. Temperature was subnormal, respirations 28, pulse 108. A physician diagnosed probable appendicitis, and sent the boy to a local hospital for operation at 7 A. M., March 5. Immediately after admission a urinalysis showed heavy sugar and acetone and the diagnosis was changed to impending diabetic coma. Fluids and 4 drachms of sodium bicarbonate produced no perceptible change, and consultation was called with a view to the use of insulin.

When seen at 10 A. M. the boy was in acute distress, stuporous but able to answer questions when sufficiently roused. Dyspnea was not

TABLE 18

Case No. 1346

Date 1923	Hour	Diet		Urine				Blood Plasma			Sodium Bicarb. Gm.	Insulin, Units	Remarks
		P Gm.	C.H Gm.	Vol. cc.	Glycosuria Gm.	Nitroprusside	$FeCl_3$	Sugar Mg. per 100 cc.	Nitroprusside	CO_2 Cap. Vol. %			
Mar.													
5	10.00 a.m.	...	...	...	...	...	....	714	++++	21.4	...	15	Intravenously.
	10.10	...	12	...	...	...	....	....	....	....	5	35	
	10.45	...	6	...	++++	++++	++++	...	....	..	...	25	
	11.45	...	...	....	....	....	....	....	....	..	..	25	
	11.50	...	18	....	....	....	....	577	++++	29.	3	..	Vomited
	2.00 p.m.	...	..	....	....	....	....	....	....	....	...	25	
	2.30	...	...	....	....	....	....	....	....	....	...	..	Vomited.
	3.30	4	24	...	....	....	....	405	..	40.4	...	..	Pulse 142. Respirations 26
	4.30	..	..	....	....	....	..	....	....	....	...	25	Pulse 128. Respirations 24.
	5.20	...	..	....	....	....	....	460	++++	39.5	...	..	Very drowsy, listless; refused food and water.
	6.00	...	24	....	....	....	....	....	....	....	...	50	Pulse 130. Respirations 24. Lapsing deeper into coma.
	7.00	..	..	700	++++	++++	++++	....	+++	....	...	..	Drowsy; face flushed; not able to sit up
	7.40	..	..	....	....	....	..	....	....	....	...	40	Refuses to take food and water. Vomited.
	8.00	...	10	....	....	....	..	....	....	....	...	..	Sleeps constantly.
	9.00	...	10	....	....	....	..	....	....	....	...	..	Drowsy, weak, fatigued.
	10.00	...	..	....	....	....	..	300	++++	52.8	...	..	Nauseated.
	11.00	...	30	....	....	....	..	....	....	....	...	30	Able to sit up when persuaded
	12.00 m.	...	..	300	+++	+++	+++	..	..	....	...	..	Nauseated.
6	3.00 a.m.	...	18	....	..	....	....	..	....	....	...	25	Vomited.
	5.50	...	..	155	+	+	+	..	....	....	...	..	
	6.00	...	30	....	..	....	....	..	....	....	...	..	
	7.00	...	..	....	..	....	....	..	....	....	...	40	
	7.30	20	30	95	0	0	0	60	+	58.	5	..	Greatly improved; ate breakfast.
	8.00	...	25	....	..	....	..	....	....	....	...	..	
7	.....	90	160	2250	139.90	....	....	139	....	90.	...	15	
8	.....	100	200	3400	179.52	....	....	263	....	72.	...	26	
9	.....	"	"	2100	58.40	....	....	263	....	....	...	24	
10	.....	"	"	2100	89.70	....	....	429	....	60.5	...	24	
11	.....	"	"	1700	45.90	....	....	....	....	....	...	24	
12	.....	"	"	....	....	....	....	....	....	....	...	24	
13	.....	"	"	....	....	....	....	268	....	....	...	..	

extreme, perhaps because of the soda. The skin was dry and pale, with a faint pink flush over the entire face and neck. Temperature 98, pulse 88, respiration 20, very deep.

A blood sample was immediately taken and 15 units of insulin injected through the same needle, and a subcutaneous injection of 35 units given as soon as possible thereafter. Carbohydrate was given in the form of orange juice, also 5 gm. of sodium bicarbonate by mouth. Water was given to capacity. Within 45 minutes there was no improvement in the patient's general condition, so 25 more units of insulin were given subcutaneously, and 25 units one hour later. The chemical findings and schedule of treatment are shown in Table 18.

As the issue was still seriously in doubt at 4:30 P. M., the patient was transferred by ambulance to the Physiatric Institute for closer laboratory control. Here he seemed to sink gradually deeper into coma, therefore resort was had to larger doses of insulin, namely, 50 units at 6 P. M. and 40 units at 7:40 P. M. From 6 to 10 P. M. he was practically in coma. He did not recognize his parents, and vomited several times, retaining none of the fluid which was given by force. At 11 P. M. 30 units of extract was given, and by 11:30 P. M. slight improvement was noticed. He was able to sit up and drink water and orange juice when persuaded. The laboratory tests showed corresponding improvement. 25 units of insulin was given at 3 A. M. and 40 units at 7 A. M. The boy then ate breakfast with relish, though weak and fatigued.

It is noteworthy that in this case not only was a total of 335 units of insulin given to a 10-year-old boy without a sign of toxic effect, but apparently smaller dosage would have been inadequate to save life.

Case No. 1348. (Diabetic coma treated unsuccessfully with insulin.) Female. American. Age 64 years. Height 5 feet 4 inches. Weight 135 lb. maximum, 110 lb. before coma. Admitted to Overlook Hospital, Summit, N. J., March 8, 1923. Family and personal history negative. The patient was always a strong and healthy woman and never had any serious illness.

Twelve years ago a diagnosis of diabetes was made by her family physician, when weakness, constipation, fatigue and thirst had been noticed for about a month. The urine was said to have contained unusually large quantities of sugar. On a restricted diet, glycosuria subsided for a short time, but it has been present during the greater part of the 12 years on a badly planned diet including large quantities of gluten bread, milk, meats, vegetables and fruits. Her body weight for the first five years remained almost stationary at 135 lb., but during the last seven years has gradually declined to 120 lb. Though weakness has increased, she has remained able to perform the entire housework for her husband and three children.

Ten days ago she became drowsy and remained in bed the greater part of the time. She was nauseated and vomited several times, but also was very thirsty, passed large quantities of urine, and had a ravenous appetite for carbohydrate. She has lost 7 lb. in the past 10 days. At 6 P. M. on March 7 she began to be very short of breath, and complained of inability

TABLE 19

Case No. 1348

Date 1923	Hour	C.H. Gm.	Urine				Blood Plasma						Sodium Bicarb. Gm.	Insulin, Units	Remarks
			Glucose	Nitroprusside	$FeCl_3$	Sugar %	Sugar Mg. per 100 cc.	NaCl Mg. per 100 cc.	CO_2 Cap. Vol. %	Total Acetone Mg. per 100 cc.	Nitroprusside	Urea Mg. per 100 cc.			
Mar. 8	10.50 a.m.	20	++++	++++	++	3.70	638	601	25 2	40 3	++++	20	...	25	Intravenously.
	10.55	17	..	....	..	....	...	..	.....	.....	.....	..	..	25	Subcutaneously.
	11.40	25	..	....	..	....	...	..	.....	.....	.....	..	..	.	
	11.45	25	..	....	..	....	...	..	.....	.....	.....	..	5	..	Improved slightly.
	12.35 p.m.	35	....	....	..	....	...	...	.....	.....	.....	..	...	..	Sat up in bed.
	12.40	.	..	....	..	....	600	...	27 1	.....	++++	18	...	..	
	1.15	..	..	....	..	....	...	...	.....	.....	.....	..	5	35	Suddenly drowsier and weaker.
	1.50	.	..	....	..	....	698	...	22 3	.....	++++	12	...	25	
	2.15	..	....	....	..	....	...	...	.....	.....	.....	..	...	..	Semi-comatose. Sinking.
	2.25	.	..	....	..	....	...	...	.....	.....	.....	..	...	50	Vomiting, and unable to retain fluids.
	3.15	.	..	....	..	....	...	...	.....	.....	.....	..	...	50	
	3.45	.	.	....	..	....	...	...	.....	.....	.....	..	...	50	Poor condition.
	4.45	.	.	....	..	....	...	...	.....	.....	.....	..	...	50	Condition unchanged.
	5.30	50	.	.	..	. .	340	. .	30.9	...	++++	..	5	..	20 gm. levulose, 20 gm. glucose, 5 gm. $NaHCO_3$ intravenously.
	5.45	..	..	....	..	....	...	...	.....	.....	.....	..	...	50	
	6.15	.	++++	++++	++	2.64	...	...	.....	.....	.....	..	...	..	Vomiting frequently.
	7.30	.	..	....	..	....	400	...	32 8	63 1	+++	40	..	50	Condition poor. Restless. Drowsy.
	7.45	..	..	....	..	....	...	...	.....	.....	.....	..	8	50	
	9.00	.	..	....	..	....	...	...	.....	.....	.....	..	...	..	Weak, drowsy, nauseated.
	9.45	50	....	....	.	....	230	606	32 7	.....	++	30	...	25	
	11.30	..	....	....	..	....	...	...	.....	.....	.....	..	...	..	Vomiting.
9	3.00 a.m	..	....	....		....	...	...	.....	.....	.....	..	5	..	Taking water and fruit juices.
	5.30	.	.	....	..	....	...	...	.....	.....	.....	..	...	..	
	6.00	50	.	.....	..	....	...	...	.....	.....	.....	..	...	..	Clinically much improved. Clear mentally.
	6.55	30	.	....	..	....	...	...	.....	.....	.....	..	...	.	Patient died.
	7.05	..	.	....	..	....	...	...	.....	.....	.....	.	...	.	

to get enough air. She had lost appetite, was constipated, and vomited several times when she attempted to take sodium bicarbonate by mouth. She was very thirsty, and was able to retain water and milk. In this condition she was admitted to Overlook Hospital at 2 o'clock in the morning of March 8, 1923.

When seen there in consultation at 10:45 A. M., the respirations were 24 and the pulse 104. Breathing was labored and stertorous. She could still be roused briefly and partially, but lapsed again quickly into sleep. There were the usual acetone breath, dry skin, and a marked flush over the cheeks, chest and shoulders. The urine showed heavy nitroprusside but very faint ferric chloride reactions.

A blood sample was immediately taken and 25 units of insulin injected through the same needle, followed by 25 units subcutaneously. The laboratory findings and later insulin injections are shown in Table 19. Clinically, the case appeared to be much more serious than indicated by the plasma bicarbonate, which was probably elevated by 10 gm. of sodium bicarbonate which had been given and retained 4 hours previously. At 11.40 the patient took a definite change for the better. She was clearer mentally, her respirations dropped to about 18 per minute, and she sat up in bed. 5 gm. of sodium bicarbonate was given by mouth. At 12:40 the plasma sugar had fallen slightly to 600 mg. per 100 cc., and the plasma bicarbonate content had risen slightly to 27.1 vol. per cent. The improvement continued until 1:15 P. M., when the respirations again became rapid and stertorous and for a time it appeared as though she would lapse into profound coma. 35 units of insulin were administered subcutaneously, and another dose of 25 units at 1:50. Because of the critical condition, the patient was transferred to the Physiatric Institute for closer laboratory control, and the trip by ambulance was borne uneventfully as usual. At 2:15 P. M. a third blood specimen showed a fall in the plasma bicarbonate to 22 vol. per cent. and an increase in the plasma sugar to 698 mg. per 100 cc. The nitroprusside reaction of the plasma had become heavier in spite of the fact that 110 units of extract had been administered. Between the hours of 2:25 P. M. and 4:45 P. M., 200 units of insulin were administered in four doses of 50 units each. The patient's clinical condition seemed unchanged for either better or worse. Her respirations were deep and stertorous, she was very drowsy, vomited four or five times, and was unable to retain anything given by mouth. By 5.30 P. M. she was definitely weaker and somewhat comatose, though barely able to respond to questions. 20 gm. of levulose, 20 gm. of glucose and 5 gm. of sodium bicarbonate were given intravenously. 50 units of insulin were given at 5:45 P. M. A urine specimen secured showed 2.64 per cent. glucose and heavy nitroprusside and faint ferric chloride reactions.

From 6:15 to 11:30 P. M. the patient was restless, though drowsy and weak. The breathing was rapid and deep, and the odor of acetone could still be detected. She was still unable to retain fluids, and vomited a dark brown material frequently. The laboratory findings improved slightly, as shown in the table. From 11:30 P. M. on March 8 to 5:30

A. M. on March 9 she rested fairly comfortably, took small quantities of water by mouth, and was listless but conscious. The respirations averaged 34 per minute, and were shallower and quieter than formerly. At 5:30 A. M. the patient was definitely improved; she was clear mentally and was able to take water, orange juice and glucose by mouth. The respirations were rapid and the pulse 118 per minute. She lay quietly in bed, recognized and spoke to her children and nurses, and had no complaint except of oppression over the chest. Her recovery seemed practically assured. At 6.55 A. M. she drank 200 cc. of orange juice with glucose with apparent relish. Without warning at 7 A. M. the pulse became suddenly weak, lips and face cyanotic and respirations shallow, and death occurred at 7:05 A. M.

A total of 485 units of extract was given in the 24 hours. As no blood sample was obtained near the end, and as the plasma sugar had been falling previously, there is no positive proof that death was not due to hypoglycemia. The lack of symptoms and the abrupt termination are opposed to this assumption, and seem rather to rank the case among the examples of sudden death which have been well known under all treatments of coma.

Case No. 1366. (Diabetic coma, with fatal termination in spite of insulin.) A woman aged 33 years was seen in consultation January 27, 1923. The family history was negative except for diabetes in a maternal uncle. The patient had a healthy life except for childhood diseases and dysmenorrhea, for which she was twice curetted. There has been some increase of thirst and urine during the past year, but this was ignored and the patient considered herself entirely well until she recently ceased to menstruate, and examination disclosed glycosuria. Following the diagnosis of diabetes on January 24, the patient was greatly worried. Her physician changed her diet by excluding most of the carbohydrate and allowing her to have protein and fat. About 3 A. M. on January 27 he was called again because of abdominal pain, dyspnea and weakness. He recognized the signs of impending coma, and gave soda, fruit juices and abundant fluids. Nevertheless, she gradually lost consciousness during the following few hours, and when seen at 10 A. M. was completely comatose and impossible to rouse. Liquids placed in the mouth were swallowed and retained. There was marked tympanites, which was not relieved by enemas or rectal tubes. No urine had been voided. Catherization yielded 30 cc. clear straw colored urine, containing much albumin and many casts, with sugar 1.77 per cent. and only slight ferric chloride and nitro-prusside reactions. The plasma gave an extremely heavy nitroprusside reaction.

It was necessary to carry out treatment with only the guidance of such tests as could be performed immediately at the patient's house. Immediately after taking the first blood sample, 50 units of insulin was given intravenously at 10 A. M. Doses of 50 units were given subcutaneously at 10:45 A. M., 11:50 A. M., and 1:30 P. M., making 200 units given in all. In addition, 400 cc. of orange juice and 60 gm. of glucose, also 15 gm. sodium bicarbonate and about a litre of water were given by stomach and retained.

Enemas aggregating 10 gm. sodium bicarbonate in one quart of saline solution were partly retained. Consciousness was not recovered, and death occurred at 3 P. M. Analyses of the blood plasma showed the following.

	Sugar Mg. per 100 cc.	NaCl Mg. per 100 cc.	Urea Mg. per 100 cc.	Bicarbonate Vol. %	Nitroprusside	Total Acetone Mg. per 100 cc.
10.00 a.m.	790	614	33	7.9	++++	74
11.45 a.m.	790	640	37	10.9	++++	..
1.15 p.m.	1072	610	48	23.3	++++	61

Abundance of carbohydrate was given in this case, in the belief that it was relatively harmless and as a precaution against hypoglycemia from the use of maximum insulin doses without immediate laboratory control. Not only hyperglycemia but also acidosis persisted, and the coma ran an unusually rapid fatal course both before and after the insulin administration, with no perceptible clinical change on account of the insulin. The very low plasma bicarbonate, tympanites and anuria probably indicated a hopeless case under any circumstances. The question of concealed infection must be considered more seriously than heretofore in such cases.

Case No. 1379. (Mild senile diabetes, with gangrene of toe. Failure of insulin treatment due to inaccurate management.) Another patient seen in consultation was an elderly woman with a typical history of neglected mild diabetes, probably of very long duration. A small infection of the great toe had penetrated so as to involve the bones and tendons, and the attending surgeon in three minor operations had removed the entire toe. In addition, the second toe had recently suffered a superficial burn from a hot water bottle. The reports showed continuous mild glycosuria without acidosis on a liberal unweighed diet. The wounds in the foot were sluggish, not seriously infected, but of the kind which would ordinarily not heal on diet treatment. Favorable features were the excellent general strength and the existence of good pulsation in the arteries of the ankle and foot. Temperamentally, the patient and her household seemed unsuited for rigid restriction of diet. An attempt was therefore made to answer several questions: first, whether insulin could accomplish healing of the wounds in such a case; second, whether the patient might thus be spared undernutrition, the more generous diet being perhaps one factor in the improved healing hoped for; and third, whether these results could be attained in a case of mild diabetes without weighing the diet.

For these purposes, a fixed plan of diet was mapped out, the quantities of food being not weighed but estimated according to the size of the various helpings, so as to insure against any great variations from day to day. The surgeon in charge was supplied with insulin, which he was to

administer personally each morning and evening. Every sample of urine voided was to be tested for sugar; over-dosage was not to be feared as long as glycosuria was present, and as soon as glycosuria ceased blood samples were to be taken which should furnish the guide to the dosage thereafter. This program was to be checked up by frequent telephone consultations.

Starting with only 1 unit, the dosage was gradually increased as high as 30 units per day. According to the laboratory reports received, the slight glycosuria, in the neighborhood of 1 per cent. or less, was not appreciably changed by the insulin. The sensitive patient objected to the pain of the subcutaneous injections, and during the last few days the surgeon changed to intravenous administration without mentioning this departure. The foot also having shown no improved healing tendency, the surgeon secretly called a diabetic consultant from another city, who placed a dietitian in charge, instituted a weighted diet, and after several weeks succeeded in stopping glycosuria without insulin. The wounds in the foot nevertheless broke down, and were treated further by conservative surgery. Insulin was used later, but the leg came to amputation as usual. With the continuous employment of a dietitian, the patient followed treatment better than anticipated, and the final outcome as respects wound healing and general health has been excellent.

This case to some extent illustrates the stubbornness of the glycosuria even in mild diabetes in the presence of any small focus of infection, so that surprisingly high insulin dosage is required, and also the failure of healing of gangrene even when the patient is sugar-free. To a greater extent it illustrates the impossibility of achieving success even with insulin unless provision is made for accurate management.

Case No. 2071. (Severe diabetes. Lipemic tendency. Influence of carbohydrate and protein.) Male. American. Age 50 years. Height 5 feet 9 inches. Weight 175 lb. maximum, 121 lb. at admission, May 28, 1922. Family history negative except for diabetes in a maternal grandfather. The only important features in the personal history were bladder trouble, possibly tuberculous, 12 years ago, and the removal of a tuberculous left kidney 8 years ago. The health then appeared good until six weeks before admission, when a physician consulted because of loss of weight found 4 per cent. glycosuria. The condition remained uncontrolled until he was referred to the Institute.

At admission, heavy glycosuria, ketonuria, lipemia, plasma sugar of 0.750 per cent., plasma bicarbonate of 32.8 vol. per cent., and signs of impending coma were present. The acute danger passed off with the usual treatment. On a diet of 30 gm. protein and 5 gm. carbohydrate, the urine still contained sugar on June 10, but became clear after two days of fasting. Continuance of the same or lower diets to July 1 was necessary in order to reduce the plasma sugar to normal. The weight rose by invisible water retention to 125 lb., and the strength, though reduced, was much better than at admission. The diet was gradually increased to 60 gm. protein, 25 gm. carbohydrate and 1200 calories, on which the patient

was discharged August 11, 1922, with plasma sugar of 0.117 per cent. at a weight of 130 lb. At home, the progress was unsatisfactory, owing to the patient's tendency to add slightly to his diet in order to increase his strength for work. Hyperglycemia was shown in all tests, and was followed as usual by glycosuria. The patient was readmitted March 4, 1923, with heavy glycosuria, slight ketonuria, heavy lipemia, and plasma sugar of 0.370 per cent. A diet of 60 gm. protein, 25 gm. carbohydrate and 1200 calories was instituted, and insulin treatment was begun March 9 with 8 units daily. The detailed record is shown in paper No. 2 (Table 10). The tendency to lipemia has been one feature of the case. With glycosuria absent and with hyperglycemia between 0.2 and 0.3 per cent., on such a diet as 60 gm. protein, 100 gm. carbohydrate and 62 gm. fat, the plasma has continued to be moderately turbid with fat even in samples taken before breakfast.

The patient was discharged March 28, 1923, on 100 gm. protein, 100 gm. carbohydrate and 2000 calories with 15 units of insulin per day, and remained free from glycosuria for one week. Increase in diet to 2400 calories caused sugar to appear in the morning urine tests, while hypoglycemic reactions occurred in the evenings. This condition was partially remedied by adding 3 units of insulin to the morning dose. He had gained in weight to 130 lb. on April 25. Accurate adjustment of diet and dosage is difficult in a patient living at a considerable distance and in unfavorable environment, but he is infinitely better off in all respects than without insulin.

Case No. 2127. (Severe juvenile diabetes, following infections. Improved condition and tolerance with insulin.) Female. American. Age 4 years. Height 3 feet 1 inch. Weight 29 lb. at admission, Aug. 19, 1922. The family history was negative except for diabetes in a cousin of the father. The child was entirely well until she had scarlet fever complicated by nephritis in February, 1922. Albuminuria ceased in four months. She was vaccinated on the left thigh July 15, 1922, and within a week developed thirst and polyuria. The diagnosis of diabetes was made three days later, and a very low carbohydrate diet without limitation of protein or fat failed to control it. Between July 25 and August 10 she lost 9 lb., and on August 18 became drowsy.

The acidosis cleared up quickly on routine treatment. The food tolerance proved to be very low, so that up to October 17 no more than 300 calories could be tolerated, at a weight of 27 lb. This weight was partly due to edema, and the child was actually very emaciated and weak. Increase of the diet to 350 calories resulted in a gradual increase of hyperglycemia up to 0.375 per cent. on Nov. 1, when insulin treatment was begun. The patient was discharged Jan. 14, 1923, free from glycosuria, on 40 gm. protein, 40 gm. carbohydrate, 780 calories, and 12 units of insulin per day. Her weight had risen to 32 lb. without edema, and her strength was correspondingly improved.

At home she has remained continuously free from glycosuria and with a tendency to low blood sugars which have been responsible for slight

collapse symptoms on a few occasions. It has been possible gradually to increase her diet to 70 gm. protein, 65 gm. carbohydrate and 1650 calories without changing the dose of insulin. The weight has risen to 44½ pounds. It had been impossible to build up more than a minimum tolerance by five months of strict undernutrition treatment, but these results in four months of insulin treatment may be interpreted to indicate a decided rise of tolerance, though no tests of the assimilation without insulin have yet been made.

Case No. 2159. (Mild senile diabetes, with post-operative infection and intoxication. No benefit from attempted use of insulin under inaccurate conditions.) Male. Hebrew. Age 76 years. Seen in consultation October 16, 1922. His son has been diabetic for many years. Otherwise the history is negative. Notwithstanding his age, the patient has been an active business man up to about six months ago, when symptoms of thirst, polyuria, and loss of weight became known to the family. The patient would not permit a urinalysis or take any precautions. In October he began to suffer from frequent scanty micturition due to retention. His physician diagnosed enlarged prostate, ordered him to a hospital, and is said to have obtained nearly two litres of urine by catheter. Sugar was found present, and was not controlled by the lax dietary restrictions. Slight fever developed, and on October 11 suprapubic cystotomy was performed. The wound gave no trouble locally, and the patient continued to eat, but weakness became noticeable and acetone and acetoacetic acid appeared in addition to the sugar. When seen on October 16, the patient had neither dyspnea nor drowsiness, the temperature ranged about 100 to 101 degrees F., but the appearance was what is generally called "toxic." A fat-free diet of 40 gm. protein and 60 gm. carbohydrate was prescribed, together with insulin increasing from 10 units to 40 units per day, with a few intermissions because of lack of insulin. In several blood analyses, the plasma sugar approximated 0.4 per cent., and the CO_2 capacity, urea and other analyses were normal. Insulin showed no appreciable influence upon the glycosuria or the general condition. Subsequent statements from the family indicate that the diet was not accurately carried out. Death occurred November 2 from sepsis, without symptoms of diabetic coma.

Insulin could not have changed this result under the hopeless conditions, but the case illustrates the inadequacy of moderate doses to control glycosuria in the presence of infection.

Case No. 2165. (Moderate diabetes. Failure of gangrene to heal with insulin. Persistence of hyperglycemia. Successful amputation and improved nutrition.) Male. Italian. Age 72 years. Height 5 feet 4½ inches. Weight 200 lb. maximum at the age of 68, 172 lb. at admission, Nov. 13, 1922. The family history was negative. The patient was always healthy and strong, and had no illness except childhood disorders. Diabetes began acutely 11 years ago with polyuria and polydipsia. The diagnosis was made immediately, and symptoms immediately subsided with restriction of carbohydrate only. He relaxed diet shortly after-

wards, but had no complaints or symptoms until 3 years later when he developed intense pruritus, which his physician told him was due to glycosuria. He resumed a diet of meats, vegetables, gluten bread, buttermilk, butter and cream, without becoming free from glycosuria. Seven years ago bilateral cataracts were diagnosed. Vision gradually grew dimmer for three years, when the cataract of the left eye was extracted. The operation was not successful on account of post-operative hemorrhages. Vision was poor, and it was only with the aid of a high power magnifying glass that he could read. The right eye has never been operated upon. Two years ago he was told that his blood pressure was high. Several readings than were found above 190 systolic, but during the past year the pressures have not been more than 170 systolic. His chief complaint has been numbness and pain in the left foot below the ankle, for the past six weeks. He has had cramps in the leg, especially at night, which prevented him from sleeping. The foot has felt numb and cold. For the past two weeks the great toe has been very painful and hypersensitive to heat and cold. Three days ago a small brown spot appeared on the outer surface of the great toe.

The patient is a well developed elderly male of massive osseous structure and broadly developed musculature. He is well nourished, with considerable adipose tissue over the whole body, particularly over the abdomen. There is a peculiar pasty pallor of the skin. He is entirely blind in the right eye. in which the pupil is irregular and an advanced cataract present. The pupil in the left eye is also irregular, and there are a few remaining scattered opaque masses of fibrous tissue adhering to the lens capsule. Vision for distant objects is good, and he is able to read newspaper print with the aid of a large lens. Lungs and heart are normal. Blood pressure 170/90. Temporal vessels are tortuous, and radials and brachials are thick and sclerotic. He complains of pain and numbness of the right foot. No pulsation can be felt in the dorsalis pedis artery. The toes are very cyanotic when the foot is held pendant. There is a brown circular indurated area 1 cm. in diameter on the lateral surface of the left great toe. There is no evidence of active infection.

From admission on Nov. 12 to Dec. 8, the patient was treated without insulin. During three weeks the diet averaged only 40 gm. protein and 15 gm. carbohydrate per day. He was thus kept free of glycosuria, but the blood sugars were always above 0.2 per cent. The body weight was reduced from 172 to 158 lb. As the superficial gangrenous area of the toe did not improve, on Dec. 8 the use of small doses of insulin was begun, namely 2 units twice daily, with the hope of hastening healing. On Jan. 16, 1923, the dosage was increased to 3 units twice daily, and the diet in the meantime increased gradually to 55 gm. protein, 10 gm. carbohydrate and 1000 calories. He was free of glycosuria at all times, but on the higher diet hyperglycemia of over 0.2 per cent. was still present. The deficiency of insulin indicated by hyperglycemia is confirmed as usual by this resistance to small doses. On Jan. 22 the foot and toes became painful, especially at night, and two days later the gangrenous area increased in size and discharged a small amount of blood tinged pus. It

TABLE 20
Case No. 2165

Date 1922	Diet			Urine		Blood Plasma			Insulin, Units Per Day	Body Weight, Lb.
	P. Gm.	F. Gm.	C.H. Gm.	Glucose	Nitro-prusside	Sugar Mg. per 100 cc.	NaCl. Mg. per 100 cc.	Blood Urea. Mg. per 100 cc.		
Nov.										
12-13	45	5	10	...	...	...	...	...	...	...
14	45	19	10	...	++	246	589	42	...	172
16-18	45	17	10	0	++	184	...	...	...	169
19-20	45	23	20	0	++	217	...	...	...	163
21-26	45	24	20	0	+	242	...	...	...	160
27-30	40	18	5	0	+	226	...	...	...	158
Dec.										
1- 5	40	20	15	0	0	206	...	...	...	158
6- 8	40	6	15	0	0	199	...	...	4	...
9-11	40	16	15	0	0	...	...	...	2	...
12-20	40	18	15	0	0	238	...	...	4	...
21-26	40	18	15	0	0	209	...	...	4	...
27-31	40	53	15	0	0	211	...	...	4	148
1923										
Jan.										
1- 7	40	53	15	0	0	...	...	...	4	149
16	37	55	7	0	0	...	...	...	6	...
17-18	66	82	10	0	0	...	...	...	6	147
19-21	55	92	10	0	0	180	...	...	6	145
22-28	55	82	10	0	0	160	...	...	6	142
29-31	60	97	20	0	0	160	...	...	6	142
Feb.										
1	60	97	20	0	0	182	601	32	6	141
2- 3	60	74	70	0	0	192	573	40	6	146
17-21	60	44	17	0	0	180	...	...	10	...
22-28	80	151	80	0	0	...	...	...	10	...
Mar.										
1- 3	80	151	80	0	0	192	589	38	15	...
4- 8	100	177	100	0	0	189	...	...	18	...

gradually increased, so that by Jan. 29 the whole toe was involved and small lines of lymphangitis began to appear over the dorsum of the foot. By Feb. 1 the whole of the great toe was red, swollen and painful, and 24 hours later there was marked cellulitis of the whole foot. Though arterial pulsations could not be felt anywhere about the ankle, the pulsation of the popliteal artery was good. Amputation of the left leg below the knee was performed on Feb. 5 under nitrous oxide anesthesia in another hospital. There was considerable shock following the operation, but within 48 hours he was able to be up in a wheel chair. The diet after the operation was 60 gm. protein. 90 gm. carbohydrate and 1400 calories. Glycosuria was present for the first three days, but gradually disappeared when insulin was increased from 6 units to 10 units. Since the operation he has been kept entirely free of glycosuria and the blood sugars have been kept approximately normal. Healing has taken place rapidly, considering the age of the patient and the advanced arteriosclerotic condition. By March 8 the wound was entirely healed with the exception of a small superficial granulating area about 2 cm. in diameter. At the present time he is tolerating a diet of 100 gm. protein, 100 gm. carbohydrate and 177 gm. fat without glycosuria. He has gained greatly in strength and has no complaints. The results are in all respects similar to those obtained heretofore with strict diet treatment, except that a higher level of nutrition is made possible by insulin.

Case No. 2166. (Mild diabetes and obesity. Refractory hyperglycemia. Experimental doses of insulin.) Female. Jewish-American. Age 55 years. Height 5 feet 1 inch. Weight 260 lb. maximum ten years ago, 145 lb. at admission, November 7, 1922. The most of the family are more or less obese, but no other case of diabetes has been known. The patient's six children are all obese. The personal history was unimportant except for over-eating and sedentary life. Glycosuria and loss of weight have been practically continuous for the past ten years. It is not known how much longer the duration of the diabetes may have been. At admission, the patient looked well and had no complaints except loss of weight and slight weakness.

Glycosuria was heavy and acetonuria moderate. On a diet of 40 gm. protein, and 5 gm. carbohydrate for five days the glycosuria ceased, but the plasma sugar remained practically unchanged at 0.283 to 0.297 per cent. The acetone reactions were practically unchanged. A diet of 60 gm. protein and 20 gm. carbohydrate for three days reduced the acetone to traces, but raised the plasma sugar to 0.319 per cent. and brought back moderate glycosuria. The urine then cleared on a diet of 40 gm. protein and 10 gm. carbohydrate, though small amounts of acetone continued to return from time to time. From Nov. 30 to Dec. 28 the diet was only 30 gm. protein and 12 to 18 gm. of fat per day, without carbohydrate or other materials except the usual non-nutrients which served to prevent hunger. The patient remained comfortable, and on account of invisible water retention the weight fell only to 140 lb., after having gone as high as 150. Glycosuria was constantly absent, but the plasma sugar remained

stubbonly and invariably between 0.206 and 0.272 per cent. Beginning Dec. 29, the diet was built up rather rapidly, and the patient was discharged Jan. 14, 1923, free from glycosuria and ketonuria on 50 gm. protein, 20 gm. carbohydrate and 1500 calories, at a weight of 132 lb. and with plasma sugar of 0.220 per cent.

The case was recognized from the outset as one of mild diabetes with stubborn hyperglycemia, which is a fairly common phenomenon with long-standing cases of this type. It has previously been pointed out[13] that such hyperglycemia has caused confusion because of its occasional association with nephritis or hypertension. This patient was free from albumin and casts and from any evidence of arteriosclerosis. At admission, the blood pressures were 110 to 120 systolic, 60 to 76 diastolic, the blood urea 14 mg., and the plasma chloride 577 mg. per 100 cc. It has never been the policy of this Institute to require normal blood sugars in these cases with very slight progressive tendencies. The rigid undernutrition was carried out because the patient needed reduction of weight as well as the building up of tolerance. She desired these results in the shortest time and had no complaint of the diet. The opportunity was taken to observe the effect of small doses of insulin in such an inherently mild case. One unit of insulin was given on Dec. 11, 2 units daily from Dec. 12 to 16, and 4 units daily from Dec. 17 to 19. On a typical day, Dec. 17, a blood sample showing 0.270 per cent. plasma sugar was taken and a dosage of 2 units of insulin given before breakfast. The plasma sugar reached its minimum at 11.30 A. M., with 0.189 per cent. by Benedict and 0.186 per cent. by the Folin and Wu method. The evening doses of 2 units before supper did not reduce the usual morning hyperglycemia, so that on the whole the effect upon the blood sugar was insignificant even with the prolonged semi-starvation and the dosage of 4 units per day. As the differences between the Benedict and the Folin-Wu readings were never great and a marked though brief reduction followed the insulin injections, it is believed that the figures indicate true plasma sugar and not interfering substances. Acidosis at this time was represented only by slight to moderate nitroprusside reactions with negative ferric chloride reactions in the urine, and with negative nitroprusside tests and normal CO_2 capacity in the plasma. As the hyperglycemia in this and similar cases has continued after acetonuria has altogether ceased, the latter can scarcely be considered responsible. With the very low diet, which was lacking in carbohydrate for the combustion of acetone bodies, the insulin showed no tendency whatever to reduce the acetonuria. It seems evident that a surprisingly large insulin dosage would be required to maintain normal blood sugar in such a case, and yet the patient was soon able to tolerate 1500 calories with no immediate increase of hyperglycemia. As a fair number of islands of Langerhans are usually found at autopsy in such cases, the persistent hyperglycemia and the slight tendency to downward progress are perhaps both explainable by a speculative hypothesis that the injury of the islands is of such character that their response to functional stimuli is subnormal.

Case No. 2186. (Extremely severe diabetes. Suggestion of possible minimum insulin requirement of adult.) Female. American. Age 30 years. Height 5 feet 2¼ inches. Weight 118 lb. maximum, 69 lb. at admission, Dec. 2, 1922. Family and personal history negative. Diabetes began three years ago and has run a severe course with very little treatment. At admission, she showed extreme emaciation and weakness, intense glycosuria and acetonuria, and plasma bicarbonate of 18.5 vol. per cent.

TABLE 21

Case No. 2186

Date 1922	Diet				Glycosuria Gm.	Plasma Sugar Mg. Per 100 cc.	Weight, Lb.	Insulin, Units
	P. Gm.	F. Gm.	C.H. Gm.	Cal.				
Dec.								
8	15	0	50	260	++++	...	80	2
9	"	"	"	"	20.42	...	...	2
10	"	"	"	"	25.88	394	81	0
11	15	0	40	220	24.00	...	...	1
12	"	"	"	"	15.07	...	83	2
13	"	"	"	"	17.00	429	...	2
14	"	"	"	"	——	...	83	4
15	"	"	"	"	17.24	...	...	4
16	"	"	"	"	——	375	84	4
17	40	3	15	250	+	...	...	4
18	40	1	15	230	0	...	85	4
19	40	8	15	292	0	...	...	4
20	40	0	15	220	0	349	88	4
21	"	"	"	"	+	...	...	4
22	40	4	15	256	+	...	...	6
23	40	6	15	274	0	300	...	6
24	40	11	15	319	0	...	86	6
25	40	3	15	247	0	...	...	6
26	40	2	15	238	0	...	85	6
27	40	13	15	337	0	326	...	6
28	40	26	15	454	0	...	83	6
29	40	11	15	319	0	283	...	6
30	40	9	15	301	0	...	84	6
31	40	11	15	319	0	...	...	6
1923								
Jan.								
1	40	9	15	301	0	...	84	6
2	40	10	15	310	0	...	...	6
3	40	12	15	328	0	357	82	9
4	"	"	"	"	0	...	...	9
5	40	10	15	310	+	395	85	9
6	"	"	"	"	++	...	...	9
7	40	9	15	301	+	...	...	9
8	40	11	15	319	+	395	...	12
9	40	8	15	292	0	...	81	12
10	"	"	"	"	0	...	...	12
11	40	12	15	328	0	349	78	12
12	"	"	"	"	0	...	...	12
13	40	18	15	382	0	319	...	12

PATIENT No. 24



August 20, 1922



April 25, 1923



August 20, 1922



April 25, 1923

PATIENT No. 823



October 28, 1922



April 10, 1923



October 28, 1922



April 10, 1923

PATIENT No. 918



August 22, 1922



January 11, 1923



August 22, 1922



January 11, 1923

PATIENT No. 1034



August 20, 1922



January 6, 1923



August 20, 1922



January 6, 1923

On a diet of 15 gm. protein and 50 gm. carbohydrate daily, the acidosis rapidly diminished without the aid of insulin. There was a further diminution following the introduction of insulin Dec. 8, and after Dec. 15 all acetone reactions were completely negative. Acidosis was therefore not an explanation of the subsequent results.

From Dec. 17 onward, the diet was 40 gm. protein and 15 gm. carbohydrate, with as little fat as convenient. Marked hyperglycemia continued, and traces of glycosuria returned in the early part of January, until stopped by increase of the insulin dosage to 12 units daily. Even with this dosage and the prolonged semi-starvation, the plasma sugar was still above 0.3 per cent. Treatment was discontinued for extraneous reasons, and the patient has not been heard from since Jan. 26, when glycosuria and plasma sugar of 0.416 per cent. were present on a diet of 40 gm. protein, 15 gm. carbohydrate and 600 calories, with 15 units of insulin per day. The final weight was 85 lb., owing to slight edema.

The case is mentioned for its unusual severity. During the greater part of the time acidosis was completely absent, also there was no sign of infection to explain the difficulty. The metabolism was evidently reduced to a very low level.

The case seems to show that a woman 5 feet 2½ inches tall and emaciated to a weight of about 80 pounds may require at least 12 units of insulin per day in order to remain free from glycosuria on a semi-starvation regime. The possible excess used above this quantity would be represented by the unknown, but evidently small, supply from the patient's own pancreas. In a broad sense, therefore, it may be deduced that in order for any adult patient to be freed from glycosuria by the most extreme undernutrition, the pancreas must be producing in the neighborhood of 12 units of insulin per day.

Case No. 2215. (Severe diabetes. Insulin requirement for carbohydrate, protein and fat.) Female. Jewish-American. Age 34 years. Height 5 feet 5⅜ inches. Weight 145 lb. maximum two years ago, 94 lb. at admission, Jan. 14, 1923. One possible case of diabetes in family. Personal history—measles and diphtheria in childhood; tonsillectomy at 17; influenza in 1917; dental caries and pyorrhea. There has been loss of weight for two years, and diabetes was diagnosed with the onset of thirst and polyuria one year ago. Limitation of diet controlled the sugar for a time, but for some six months glycosuria has been heavy and increasing, and weight and strength have been lost rapidly.

At admission, glycosuria was heavy and ketonuria moderate, and the plasma sugar was 0.412 per cent. On a diet of 30 gm. protein and 5 gm. carbohydrate, glycosuria persisted with only very slow diminution, and from Jan. 22 to 24 the sugar excretion was 17 to 25 gm. daily. With 2 units of insulin per day, the excretion fell to 3.5 gm. on Jan. 25 and ceased on Jan. 28. Further details are given in paper No. 2 (Table 20).

The patient was discharged March 25, 1923, on 100 gm. protein, 100 gm. carbohydrate and 2500 calories, with 12 units of insulin per day. Her weight was 92 pounds. Sugar was present in the morning urine

specimen but absent at noon and evening. She returned for an office call on April 14. Her weight had increased to 101 pounds. The urine specimen which was taken after lunch was free from sugar, but the plasma sugar was 0.416 per cent. She was advised to increase the insulin to 20 units per day. The urine then remained free from sugar, while the weight increased to 104 pounds by April 23. There have been no symptoms of hypoglycemia, and the strength and general condition are improving rapidly.

Case No. 2228. (Mild juvenile diabetes in unfavorable environment. Improved nutrition and prognosis with insulin.) Male. American. Age 7 years. Height 3 feet 1 inch. Weight 50 lb. maximum, 47 lb. at admission, Jan. 30, 1923. There is a somewhat indefinite history of recent onset of diabetic symptoms. The case was evidently mild, as the tolerance within a few days amounted to 55 gm. protein, 40 gm. carbohydrate and 1300 calories, and possibly slightly more. After discharge on Feb. 20, the progress seemed satisfactory at home, but he was readmitted Feb. 27 for insulin treatment. The weight at this time was 45 lb. and the plasma sugar 0.107 per cent. After gradual increase of diet and dosage, he was discharged March 13 on 65 gm. protein, 80 gm. carbohydrate, 1700 calories, and 6 units of insulin per day.

The child reported for office examination on March 26. The mother stated that he had been in splendid condition and was active the whole day. The urine, which was tested twice daily, was always negative for sugar. The blood specimen taken 1¾ hours after his noon meal was 0.159 per cent. The diet and insulin dosage were kept unchanged.

The problem in this case was that of a child of foreign parentage referred by a social service worker from one of the poorer districts of New York. The parents were cooperative and greatly concerned, but had very little education or knowledge of English. The mother was taught the preparation of a weighed diet, but the ultimate prognosis under the usual treatment would have been bad. Insulin was used to raise the level of nutrition with a view to growth and development and also to permit sufficient quantity and variety of food to eliminate the temptation to break diet as far as possible. Though the case was in an early mild stage, the present impression is that the prognosis has been greatly improved in all respects by insulin.

Case No. 2229. (Moderately severe diabetes. Improved nutrition with insulin. Insulin requirement for protein and carbohydrate.) Male. American. Age 24 years. Height 5 feet 11 inches. Weight 156 lb. maximum, 126 lb. at admission, Jan. 27, 1923. Family history—patient's father is obese, and a brother died of diabetes. Personal history clear except measles and mumps in childhood, and chronic dental caries and pyorrhea. A urinalysis last April was reported negative. The loss of 30 lb. weight has occurred entirely in the past three months, and examination performed for this reason two weeks ago revealed glycosuria.

On admission, the patient's complaint and appearance were of weariness and weakness. On 45 gm. protein and 10 gm. carbohydrate daily, the

glycosuria by Feb. 1 had fallen from 77 gm. to 14 gm. and was evidently about to clear up, but insulin treatment was begun to save time and avoid undernutrition. The detailed report is given in paper No. 2 (Table 8). The patient was discharged Feb. 20, weighing 131 lb., on 80 gm. protein, 80 gm. carbohydrate and 2000 calories, with 15 units of insulin divided in three injections per day. Glycosuria was absent and the plasma sugar approximately normal.

At home, the weight has remained at 131 lb., but the patient has had heavy glycosuria, probably from unintentional mistakes in diet. The insulin dosage has been increased to 21 units, and it will be necessary to try to remedy the difficulty through advice by mail. The patient has been able to resume his former occupation as a clerk.

Case No. 2230. (Incipient juvenile diabetes. Use of insulin to improve nutrition and to assist toward prophylaxis or cure) Male. American. Age 12 years. Height 5 feet 1⅞ inches. Weight 105 lb. maximum, 103 lb. at admission, Jan. 26, 1923. Family and personal history were unimportant. The boy was brought for examination because of the recent appearance of polyuria and glycosuria, which cleared up with very slight limitation of diet. The purpose in view was a more definite diagnosis as well as treatment. The patient was large, over-nourished, normal to physical examination but not rugged in appearance. The existing glycosuria and hyperglycemia of 0.357 per cent. came to normal within 24 hours, and with two weeks of observation it became apparent that a diet of 80 gm. protein, 50 gm. carbohydrate and 1800 calories was approximately the limit which could be tolerated with normal plasma sugar. An attack of grippe and tonsillitis then lowered the tolerance for the ensuing week, but the same tolerance was restored immediately afterward. Insulin treatment was next begun, and the patient was discharged March 2, 1923, on 90 gm. protein, 100 gm. carbohydrate, 2400 calories, and 4 units of insulin per day. The weight was 99 lb., and the plasma sugar was normal. At home, it has gradually become necessary to increase the insulin to 12 units daily.

The usual two principles guided the use of insulin in this incipient case; first, the provision of an adequate diet for comfort and for growth, with the definite understanding that the abundant calories were to be used up in hard exercise and no excessive body weight permitted; second, prophylaxis against downward progress and help in the direction of a cure by sparing the pancreatic function to the greatest possible extent.

Case No. 2232. (Severe diabetes. Avoidance of undernutrition by insulin.) Female. American. Age 34 years. Height 5 feet 6 inches. Weight 152 lb. maximum one year ago, 110 lb. at admission, January 30, 1923. Family history—mother and a maternal aunt obese and diabetic. Personal history—measles, mumps, whooping cough, scarlet fever, tonsillitis. Tonsillectomy four years ago. Appendectomy, curettage and perineal repair. The loss of weight has occurred during the past year. The first diagnosis was made in May, 1922. She had ignored diet until

three months ago, and since then has been lax and not free from glycosuria.

On a diet limited to 30 gm. protein, from Jan. 30 to Feb. 8, glycosuria diminished from 30.5 gm. to 1.4 gm. Though it was evidently on the point of disappearing, the use of insulin was begun to prevent further undernutrition. Glycosuria ceased immediately with 2 units, but the plasma sugar was still 0.246 per cent. on Feb. 12. The diet was then increased to 40 gm. protein, 40 gm. carbohydrate, and 680 calories, with which 8 units of insulin daily up to Feb. 20 was unable to prevent a steady increase of glycosuria to 20.75 gm. The diet was then increased to 50 gm. protein, 40 gm. carbohydrate, and 1000 calories, and the insulin to 16 units. Glycosuria ceased immediately but hyperglycemia persisted. The patient was discharged Feb. 27, 1923, on 60 gm. protein, 80 gm. carbohydrate, 1300 calories, and 20 units of insulin daily, at a weight of 114 lb. The diet has since been changed to 70 gm. protein, 60 gm. carbohydrate, and 1800 calories. The weight has risen to 116 lb., and glycosuria is still absent with the dosage of 20 units of insulin. Though the exact tolerance in this case is not known, it would undoubtedly have been found very low, and the clinical condition and prognosis are revolutionized by the use of insulin.

Case No. 2243. (Severe juvenile diabetes. Improved nutrition with insulin.) Male. Hebrew. Age 5 years. Height 3 feet 3½ inches. Weight 40 lb. maximum, 28 lb. at admission, Feb. 27, 1923. Family history is negative except for obesity in several members. Personal history unimportant. The diabetes apparently began between 1½ and 2 years ago. The patient has been treated by several physicians and in several hospitals, but has not been free from glycosuria except for short periods. He presented the typical pale, thin and weak appearance. Though glycosuria and slight ketonuria were present, the child was placed immediately on a diet of 35 gm. protein, 15 gm. carbohydrate and 600 calories, with 4 units of insulin per day. The plasma sugar was thus brought to normal within a week, though meantime the carbohydrate in the diet had been increased to 50 gm. daily. Increases were then made until the patient was discharged on March 30, on a diet of 65 gm. protein, 55 gm. carbohydrate and 1650 calories with 18 units of insulin per day. He has been kept free of glycosuria on this program and continues to gain in strength and weight.

Case No. 2249. (Impending coma cleared up by insulin.) Male. Swede. Age 30 years. Height 5 feet 10 inches. Weight 149 lb. maximum, 116 lb. at admission, March 12, 1923. The family history was negative, and the personal history negative except for chronic appendicitis in 1918, cured by operation after 4 months.

The first symptoms of diabetes were noticed on Feb. 24, 1923, in the form of thirst, polyuria, polyphagia, weakness, and pain and cramps in the arms and legs. He went to a physician on March 3, and was assured he was in good condition. He was given a few pills. The urine was not examined. The symptoms grew worse, and he could not sleep for thirst.

TABLE 22

Case No. 2249

Date 1923	Hour	C.H. Gm.	Urine				Blood Plasma				Sodium Bicarb. Gm.	Insulin, Units	Remarks
			Vol. cc.	Glycosuria Gm.	Nitroprusside	$FeCl_3$	Sugar Mg. per 100 cc.	Nitroprusside	Total Acetone Mg. per 100 cc.	CO_2 Cap. Vol. %			
March 12	8.00 p.m.	..	1450	51.9	++++	++++	349	++++	205	25.1	...	..	Vomited.
	9.00	24	....	....	....	....	...	....	...	....	...	25	Nauseated. Temp. 98. Resp. 20.
	9.30	..	.	....	....	....	...	....	...	....	5	25	
	10.00	32	....	....	....	....	...	....	...	....	...	25	
13	12.30 a.m.	..	....	....	....	....	405	++++	59	37.6	...	..	
	1.00	..	450	16.1	++++	++++	...	....	..	....	5	.	
	3.00	24	....	....	....	....	...	....	..	....	..	10	
	4.15	.	....	....	....	....	..	....	.	....	5	.	
	5.00	..	180	5.5	++++	++++	...	....	..	....	...	.	
	7.00	..	....	....	....	....	209	++	40	72.9	...	15	
	7.30	..	95	1.2	++++	+++	...	.	.	...	..	.	

On March 8 he went to another physician, who immediately diagnosed diabetes.

No acidosis symptoms other than nausea and abdominal cramps had been noticed prior to admission, but an alarming condition developed on admission, corresponding to the laboratory analyses, as shown in Table 22. Carbohydrate in the form of fruit drinks, sodium bicarbonate, and insulin made a radical change within 24 hours, as shown in the table. The insulin dosage of 100 units was low for a coma case, and recovery might have been possible under ordinary treatment without insulin.

He remained in the Institute until April 1, when he was discharged on a diet of 100 gm. protein, 100 gm. carbohydrate and 2400 calories with only 18 units of insulin per day. His weight on April 8 was 126 lb., and he was still free from symptoms.

DISCUSSION

I. General Plan of Treatment.

1. Purpose and Standards:—We have chosen as our ideal the maintenance of complete freedom from active diabetic symptoms in the form of glycosuria, hyperglycemia, acidosis, etc., as under the treatment by diet alone, together with the closest possible approach to normal nutrition, which was an impossibility in cases of any real severity under diet treatment. We are glad to note that Banting, Campbell and Fletcher[2, 3] likewise favor keeping the urine sugar-free and the blood sugar as nearly normal as possible. These standards, however, are difficult to maintain and their correctness or necessity is not yet positively demonstrated. The maintenance of continuously normal plasma sugar, which was perfectly feasible with sufficiently strict application of diet treatment, has not thus far proved possible under insulin treatment except in cases requiring only comparatively small dosage. In severe cases requiring high dosage, the margin between hyperglycemia and hypoglycemia is narrow, and the only practical way of avoiding danger from the latter has been to permit a certain degree of the former. Most writers permit not only hyperglycemia but more or less actual glycosuria, ignoring laboratory findings to this extent and confining their attention to the immediate nutrition of the patient and the avoidance of hypoglycemia. Joslin, on the contrary, has followed the conservative policy of clinging to the known benefits of undernutrition, and of using the new remedy only in the comparatively small quantities required to overcome any serious emaciation and

to keep his patients free from glycosuria with slightly less than the normal average of food intake and body weight.

2. *Institutional and Home Treatment:*—The more careful the standard of treatment that is adopted, the more necessary is a period of institutional care and training before the patient is trusted to continue the use of insulin at home. If attention be given only to the temporary appearances of well-being and if glycosuria be ignored (as many physicians doubtless will ignore it), it becomes a relatively simple matter for almost any practitioner to administer insulin to any average diabetic patient at home without even the necessity of an exact diet. All that is required is a sufficient insulin dosage to cause the patient to gain satisfactorily in weight and strength, and sufficient quantities of food, especially carbohydrate, for this purpose and for the prevention of hypoglycemia. The intermediate plan above mentioned, of permitting glycosuria to a small extent or at certain periods of the day, calls for an accurate weighed diet and nearly the same duration of institutional care as under the treatment by diet alone. The more difficult standard which we have adopted makes institutional care fully as imperative and also as long in duration as under the simple diet treatment. A liberal diet can be given quickly; but formerly we dealt with a balance between two factors, namely, the diet and the patient's tolerance, while insulin now enters as a third element in the equation. Formerly we faced practically but one danger, namely, overtaxing the tolerance, but now the opposite danger of hypoglycemia becomes important in addition. We have had satisfactory results with the treatment of two mild cases (Nos. 396 and 1156) at home under the care of nurses specially trained in the management of both diets and insulin, and in one case of moderate severity (No. 1307) the patient was allowed to go home under similar conditions earlier than we consider to be generally advisable. Unless there are exceptionally strong reasons to the contrary, we believe that patients usually receive a better start and especially a better training in the management of their condition by means of the initial period of institutional treatment.

3. *Dangers of Inaccuracy:*—The most obvious and acute danger is hypoglycemia, and the strongest warnings have been given against the use of insulin without food to furnish an adequate sugar supply or without the guidance of blood sugar analyses.

The less evident dangers are those of simple failure of treatment. The dangers from unchecked hyperglycemia and glycosuria are remote in ordinary cases, and they become acute chiefly when complications are present. It will be noticed that we tried the use of insulin in two consultation cases (No. 1379, gangrene, and No. 2159, post-operative infection) under inaccurate conditions, with a definite view to learning whether exact methods are always necessary. Both cases turned out complete failures. Another case of gangrene (No. 1336) ended fatally under treatment in the Institute when hyperglycemia and glycosuria were disregarded for the sake of nutrition. These results may possibly have been inevitable, but from comparisons between cases we have become convinced that exactness in diet and all other particulars is as essential to success as under the treatment with diet alone. There will undoubtedly be a strong tendency for physicians to take the attitude that everything possible was done in a certain case because insulin was given, and to set down a bad result as a failure of insulin treatment. The failure in a large proportion of such cases will belong not to the insulin but to the conditions under which the insulin was administered, and physicians should be prepared to assume responsibility accordingly.

4. *Character and Duration of Initial Treatment:*—As already mentioned, the very long periods of institutional care, extending into months in many of our cases, have been due either to the deficient supply of insulin and other pioneer difficulties or to the personal choice of the patient. The purpose of the preliminary period is to place the patient on a diet adequate for his nutrition, balanced by sufficient insulin dosage to provide for assimilation, and to train him for the efficient continuance of this program at home. In the majority of our patients the tolerance was already known, often for months or years previously. This information is of theoretical value, but it will probably not be necessary in practical treatment hereafter to wait to establish the severity of the case or the degree of tolerance before beginning the use of insulin. Since the supply of insulin has become adequate, numerous cases (e.g. Nos. 1029, 1319, 1332, 1344, 2229, 2232, 2243) have received insulin early for the purpose of avoiding unnecessary loss of either time or bodily weight or strength. We consider it safer as a rule to employ moderate undernutrition

at first, particularly by giving limited quantities of protein and carbohydrate and very little fat, for the sake of greater ease and safety in controlling glycosuria, acidosis and all other symptoms. After this initial control is obtained, the diet and dosage have gradually been built up in parallel under the guidance of laboratory tests. We have not attempted to plan diets according to the observed or calculated basal requirements of patients, because other factors such as muscular exercise introduce wide variations, and the plan of feeding merely what is found necessary empirically to maintain a given patient at the desired level of weight seems to be both simpler and more accurate. We have also not attempted to calculate the insulin requirement from any theoretical rules based on the glucose content of either the urine or the diet, because for reasons explained in the following papers we consider all such rules fallacious. The dosage has been worked out empirically like the diet for each individual patient. In order to do this in conformity with the standard proposed in the first paragraph above, no less than a month of institutional care seems to be desirable in most cases of any real severity. After the first control of symptoms, which now with the aid of insulin can generally be accomplished in a few days, a certain time is required for establishing the proper balance between diet and dosage and for instructing the patient in regard to both diet and insulin. Furthermore, the balance first established cannot be regarded as permanent. Increase of weight, for example, tends to increase the insulin requirement with the identical diet, while increase of the patient's tolerance may reduce the insulin requirement. To some extent adjustments to meet these changes must be made during the later home treatment of all cases, but we have preferred and patients seem also to prefer to stabilize these conditions as accurately as possible under institutional observation before they venture the change to home treatment, particularly in any distant locality.

5. *Incidental Difficulties of Insulin Administration*:—The administration by subcutaneous injection constitutes one of the first objections in the minds of both physicians and patients, but in practice this difficulty has proved to be slight. The pain is so trivial, especially with the high potency insulin now obtainable, that even the smallest children soon receive the injections without complaint. Discontinuance of the use of insulin because of

the pain (case 465) is a rarity which can be attributed only to abnormal sensitiveness and will probably be only temporary in any severe case. We have never had an infection or even a marked local reaction with this high grade insulin, and a more remarkable fact is that not a single infection has occurred among the patients giving their own injections of insulin at home.

The early samples of insulin contained appreciable traces of protein, and these gave rise to occasional sensitization phenomena, in the form either of local indurations or sterile abscesses, or local or general skin eruptions. These occurrences were few and slight, and in only one specially sensitive case in our series was it necessary to omit the injections for four days on this account. The problem of purification has been rapidly and ably solved by the Lilly Company in conjunction with the Toronto investigators, and with the improved quality of insulin we have observed no reactions whatever for the past several months, except two very slight and transitory local skin eruptions which may possibly have been due to sensitiveness to tricresol. The present insulin is said to be free from true proteins and to contain only minute traces of protein-like substances, possibly albumoses. The chemical nature of insulin itself is, of course, not yet known. Macleod[14] has reported the preparation of a protein-free insulin from fish, and Biedl's dictum that hormones are never antigens lends probability to the view that insulin is not of protein character. On the other hand, Shaffer at the meeting of the Biochemical and federated societies at Toronto in December, 1922, mentioned evidence indicating that insulin as prepared ordinarily from the mammalian pancreas is either in chemical union or in some remarkably close association with material of protein character. A very important question of the future of insulin treatment therefore rests with the chemists for decision. If insulin itself is not an antigen, it can doubtless before long be freed from antigenic impurities and its injection over unlimited periods of time should then be harmless. If, on the other hand, it shall be found that the hormone is in any way inseparably connected with material of protein character, the possible consequences of injections of even the smallest traces of an antigenic substance daily for a number of years must be viewed with some misgiving. There is no doubt that the benefits in suitable cases enormously outweigh any remote danger of this kind, but the in-

discriminate and reckless use of insulin in all sorts of cases should be discouraged.

The most important danger connected with insulin treatment at home consists in irregularities of the supply or dosage. A patient, failing to receive an expected shipment, may be without insulin for several days. Loss of appetite from infection or any other cause may raise the question of omitting or reducing insulin to prevent hypoglycemia. When patients have been kept somewhat thin, or have had their tolerance raised only to a moderate degree by moderate doses of insulin, such emergencies are easily met. By reducing chiefly the fat of the diet, glycosuria usually remains absent or slight and especially acidosis is avoided. But when a patient with severe diabetes is fattened by high diet and large insulin dosage, interruption or irregularities of treatment become extremely dangerous. Dangerous acidosis may develop with surprising quickness. The symptoms, especially at first, may be atypical and acetonuria may be deceptively slight. The diagnosis may be in doubt until a blood sample is taken, when great hyperglycemia, low plasma bicarbonate and generally a heavy nitroprusside reaction will be found. Radical treatment with insulin and other measures as used for coma will save life if used in time. *Undoubtedly many deaths will occur from this cause, however, and every physician and patient using insulin should be on guard against this danger.* The three emergencies of this kind which we encountered were all in severe cases on high diets, and fatal consequences were avoided only through the very close observation under which such patients have been kept. In any such cases the regular schedule of treatment should be restored as quickly as possible, and in the meantime there should be close clinical and laboratory observation. Any signs of acidosis should call for complete exclusion of fat and possibly a diet of carbohydrate alone.

6. Hypoglycemia:—The symptom complex resulting from undue lowering of the blood sugar was discovered and fully described by the Toronto investigators.[1, 4] We have nothing to add to this clinical picture, which appears in the form of weakness, sweating, mental disturbances in various forms (excitement, apathy, irrational behavior), and other details as described. One case of long-continued psychosis (No. 1214) was probably not attributable to insulin. Hunger has been only a rare symptom

among our patients. An extreme condition of complete unconsciousness and impending death was encountered in only one early case (No. 1194). We were taken by surprise in this instance because this patient's total dosage was only 1 unit of insulin per day, and the dose which precipitated the danger was only ½ unit. This experience illustrates the caution that must be observed in the use of only the smallest quantities of insulin in very weak and emaciated patients on very low diets. This patient evidently had so little glycogen or other available carbohydrate that this trivial dose would have proved fatal except for radical restorative measures. Macleod in a recent lecture in New York suggested that epinephrin, which has been found to be an antidote under ordinary conditions, might not be effective in extremely thin patients with minimal glycogen stores. This was the interpretation which we placed upon one of our earlier experiences, when an emaciated girl sinking gradually into unconsciousness after a small dose of insulin showed no response to a subcutaneous adrenalin injection within half an hour, but revived immediately when an intravenous injection of glucose was given. We have not used epinephrin in other cases, but have depended entirely upon rapidly assimilable carbohydrate both for use in the Institute and in our instructions to patients at home. For the ordinary mild or incipient condition, while the patient is still able to swallow, a glass of orange juice or several teaspoonfuls of glucose, corn syrup or honey stirred up in water or lemonade generally suffices to avert trouble, and may be repeated if the condition tends to return. In a more extreme stage, sugar given by stomach tube or otherwise seems to be poorly absorbed, and the effect may be slow or uncertain. In such cases, the intravenous injection of perhaps 25 gm. of glucose, in 20 per cent. or any other convenient concentration, is miraculously effective. It may be mentioned that in an acute emergency sterilization is not indispensable, for a clean filtered glucose solution injected intravenously does not cause infection. The Toronto investigators have found levulose inferior to glucose for this purpose in animals, but we have long used levulose injections to restore patients in a collapsed or dying state from hypoglycemia following unduly prolonged starvation, and in two cases levulose seemed to be as effective as glucose in intravenous injections as an antidote to overdosage of insulin. As glucose is more easily obtainable, there is no reason for using levulose. A

leading cause of hypoglycemic reactions at first was the variable potency of the early samples of insulin, so that a patient might show glycosuria with a given dose of one lot and go into collapse with the same dose from another lot. This was one of the important reasons why the general marketing of insulin was not authorized, until the Lilly Company had succeeded in the task of producing an extract which should not be subject to important variations of strength either from imperfections in the original standardization or from subsequent deterioration. The successful solution of this problem is attested by the fact that we have had no difficulty from this cause for several months past. In the adjustment of the balance between diet and dosage, many patients experience slight hypoglycemic symptoms, which are easily checked in their incipiency by a small amount of carbohydrate. We have not followed the Toronto policy of subjecting every patient intentionally to this experience, though this policy doubtless possesses safety and certain advantages. In the course of institutional treatment, every patient either experiences the symptoms in question accidentally or observes and learns about them in other patients. He thus becomes equipped for his home treatment in such a manner that tendencies to hypoglycemia have been controlled by our patients at home without difficulty or danger, by the use of carbohydrate or by omitting or reducing the doses of insulin.

7. *Quantity of Daily Doses:*—The requirement for insulin is governed by the severity of the case, the total diet, the body weight, and other known and unknown factors. For these reasons, as already stated, we have found it necessary to determine the dosage empirically for each patient as an individual. During the early scarcity of insulin, it will be noticed in a number of records that doses as low as 2 units or even 1 unit per day gave decided benefits in extremely severe diabetic cases in both children and adults. In the state of extreme undernutrition which had been necessary for the control of such cases, these doses had an effectiveness out of proportion to their size and permitted a very appreciable increase of the scanty diet. Inasmuch as these patients were producing perhaps only 4 to 16 units of insulin per day from their own island tissue, it is evident that these small injections furnished a considerable portion of their total insulin supply. As the diet, body weight and metabolism are increased,

the insulin requirement increases disproportionately, partly because several times as much insulin is somehow consumed under these conditions, and partly because the patient's pancreas is already at its maximum capacity and the entire increment of the supply must be given in the injections. In practical experience, our actual dosage for regular use, disregarding acute emergencies, now ranges between the extremes of 4 units and 70 units per day. In mild or incipient diabetes of either children or adults, it may be desirable to improve the strength and nutrition by adding perhaps 200 or 300 calories per day to the previous diet, and at first 2 units of insulin daily may suffice to keep the blood sugar normal under these circumstances. As the weight rises, this dosage gradually becomes insufficient, and ultimately the maintenance of normal conditions with this small increase of diet in mild cases generally requires between 6 and 12 units per day (cf. cases 2, 274, 337, 339, 1333, 2230). In more severe cases, the insulin requirement seems to vary partly with the individual but chiefly with the level of nutrition which is aimed at. Under any plan compatible with fair strength and comfort, it is seldom possible to treat a really severe case with less than 20 units per day. Between 30 and 50 units per day have been found necessary for most of the cases which we have regarded as severe, while the maximum of 70 units per day has been reached only in one case (No. 989) under special conditions.

8. Distribution of Doses and Meals:—The Toronto work seems to have proved that a subcutaneous injection of insulin is effective only for a few hours following its administration. An ideal treatment would supply insulin in a manner to imitate the normal pancreatic function, i. e., to some extent continuously, but with increases at times of special need. The Toronto plan of giving insulin just before meals has two advantages: namely, the insulin is thus furnished at the time when it is needed for assimilating food, and also when the food is available to prevent hypoglycemia from the insulin. It is a common experience that patients receiving large doses of insulin may begin to show hypoglycemic symptoms if the ensuing meal is delayed. In mild cases, the smaller dosage reduces the danger of hypoglycemia, and also the injections can be spaced farther apart because the patient's own pancreatic islands, if fully relieved of their burden perhaps twice a day, are able to provide for the bodily needs dur-

ing the intervening periods. We have never tried, except experimentally, to get along with only one injection per day. Even if all food in excess of the patient's tolerance be added to a single meal immediately following this injection, the fact remains that this food is only partially burned at the time and is largely stored as glycogen and other reserves, which create demands for insulin after the single dose has been used up. An experimental comparison of single and divided doses is shown in case 1308. When the total dosage has been as low as 1 or 2 units per day, we have still found it most effective when divided into at least two injections, namely, before breakfast and before supper. Convenience can often be served by giving only two doses per day in the milder cases which require only 12 to 20 units daily, and in which the patient's pancreas can be counted on to tide over the intervening periods as mentioned. In most cases of severe type, the most satisfactory arrangement is that of three doses per day, namely one before each meal. In a few cases of extreme severity, the pancreas apparently does not possess sufficient function to carry through the interval between supper and breakfast (cf. cases 918, 989, 1034, etc.). The difficulty then arises that the plasma sugar may be low in the latter part of the day, but either glycosuria or marked hyperglycemia is present in the early morning. Increase of the doses during the day may throw the patient into hypoglycemic collapse in the afternoon or evening, and nevertheless the blood sugar may be unduly high before breakfast. We have had only limited success with attempts to vary the size of doses or of meals to meet such difficulties in such cases. When the case is sufficiently severe, the giving of specially large meals with or without specially large doses either early or late in the day may change the time at which hyperglycemia and hypoglycemia respectively occur but only partially obviates the troublesome irregularities. A smoother curve might perhaps be obtained if patients would take their first meal and first dose very early in the morning, and their last meal and last dose very late at night, but most patients do not like this plan. In the most severe cases, therefore, we have resorted to the use of four doses daily at regular six hour intervals, namely, one before each of the three meals, and one at about midnight. In these cases the tendency to morning hyperglycemia has been so marked that it has usually been possible to give these midnight doses without food and with only very rare hypoglycemic symptoms, never involving the

TABLE 23

Results of Insulin Treatment in 87 Cases

Case No.	Sex	Age*	Duration* of Diabetes	Diet						Height*		Body Weight, Lb.			Present Insulin Dosage, Units per Day
				Highest Without Insulin			Highest With Insulin								
				P. Gm.	C.H. Gm.	Cal.	P. Gm.	C.H. Gm.	Cal.	Ft.	In.	Before Diabetes	Before Insulin	After Insulin	
		Yrs.	Years												
2	M	10	6	...	...	....	60	50	1400	4	2	...	50	50	9
3	F	22	7	50	5	1000	100	150	3000	5	3¼	...	78	123	60
24	M	31	10	50	10	1000	60	100	2200	5	6	140	80	90	40
54	F	44	5	45	3	800	100	112	2533	5	4	150	62	86	27
70	M	32	4	...	...	....	90	140	3500	5	9	160	110	142	40
85	M	34	8	55	10	1200	60	90	3860	5	10	165	100	122	33
174	F	45	5	50	5	800	100	100	2300	5	2	115	67	72	24
172	M	35	4	...	...	....	90	65	2500	5	8	157	115	120	18
191	M	53	17	60	10	1500	100	100	2500	5	9	165	106	104	32
200	M	56	14	...	...	....	80	50	1700	5	3	155	113	121	22
215	M	25	7	70	20	1400	70	25	2500	5	4	121	113	113	15
274	M	16	3	60	35	1600	75	40	2000	5	1⅝	120	95	104	6
314	M	58	16	50	20	1200	90	100	2500	5	10	170	131	146	20
328	M	29	5	65	20	1600	100	125	2500	5	6	155	102	103	54
337	M	21	6	65	15	1600	80	45	2000	5	6	120	91	110	12
339	F	15	3½	60	15	1400	65	25	1500	4	9	80	72	78	12
356	M	36	5	60	15	1400	90	25	1800	5	4	168	98	96	21
396	M	59	4	80	60	2800	100	100	3500	6	0	236	180	190	24
518	M	5	2	40	15	700	40	15	1600	3	7	42	37	45	21
526	M	50	7	55	5	1200	100	100	2300	5	9	177	125	155	30–45
529	F	12	3	50	10	1000	90	80	1900	4	0	56	42	56	36
539	F	9	2½	55	15	1100	100	100	1700	4	1	43	34	46	24
574	F	4½	2	20	5	350	65	60	1000	2	11	30	19	28	15
755	M	46	3	55	10	1400	100	100	2000	5	11	150	105	115	16
783	F	24	11	55	15	1000	100	100	2000	5	5	133	82	88	20

787	M	45	3	75	20	1600	100	100	2500	6	0	229	146	156	36
806	F	9	2	55	15	850	60	60	1400	4	1	50	39	47	18
823	M	27	2½	65	35	1500	55	50-150	2000	5	7	122	92	110	40-45
839	F	45	5	40	5	1000	60	100	1600	5	5	148	83	105	54
878	F	48	3½	55	10	1500	120	200	2640	5	7	126	74	98	48
918	F	5	2	10	0	120	55	80	1250	2	11½	31	22	33	16
989	F	9	2	50	15	1000	80	150	2000	4	1	47	35	61	70
1016	M	17	3½	45	10	800	80	70	2200	5	1½	90	69	85	24
1020	F	11	2	60	25	1400	60	50	1700	4	8½	75	58	60	10
1029	F	42	2	...	...	....	80	50	2400	5	2	182	109	115	10
1034	M	9	3½	0	0	0	60	100	2000	4	⅝	50	33	44	28
1044	M	48	4	...	...	....	50	10	1600	5	11	168	131	131	6
1054	F	42	5	...	...	....	50	10	1860	5	6	150	85	86	16
1065	F	16	3	...	...	....	50	40	1500	5	4	108	74	82	30
1069	F	16	2	45	10	950	80	50	2000	4	10	72	58	63	21
1073	M	27	6½	50	10	1100	90	200	3800	5	10	148	103	136	40
1075	M	15	3	40	5	800	60	20	1400	4	10	...	65	72	4
1081	M	58	2½	100	50	2000	100	250	2200	5	2½	200	127	127	4
1083	F	68	13	50	10	1100	95	85	2600	5	1	150	95	108	33
1126	M	37	9	70	35	1800	80	80	3200	5	6¾	145	130	138	10
1135	F	26	2½	60	10	1100	65	45	1800	5	4	90	65	80	21
1156	M	7	1	60	30-10	800-900	75	70	1900	3	8⅞	43	41	50	35
1167	F	11	1	30	2	275	60	35	1000	.	....	67	...	60	27
1172	F	28	1	60	20	1600	70	90	2000	5	5¼	130	76	81	16
1194	M	33	3	...	...	....	100	150	3500	6	0	145	100	124	54
1202	F	41	3	45	5	650	80	50	1800	5	1¼	142	88	95	18
1212	F	51	4	...	...	....	50	15	1200	5	3¼	118	86	86	25
1238	F	3	2	35	5	500	60	75	1000	3	0	27	24	30	12
1244	F	48	6½	...	...	....	80	45	2200	5	5⅜	130	73	80	21
1255	M	14	4	70	40	1600	70	40	2500	5	7¼	120	108	114	6
1274	M	38	1½	...	...	....	60	35	1500	5	6½	155	108	117	21
1276	F	14	2	...	...	....	80	50	1800	5	3¾	121	109	111	15
1277	M	45	4½	...	...	....	50	10	1200	5	6	150	90	90	4
1283	M	48	1	...	...	....	100	150	3500	6	¼	225	141	122	12
1286	M	52	11	...	...	....	80	100	2500	5	11	200	132	150	27
1295	F	6	½	...	...	....	60	65	1500	3	10^3_4	40	38	41	13
1303	M	6	1	...	...	....	60	50	1300	4	1	48	43	48	12
1304	M	32	1½	...	...	....	80	80	2500	5	6	128	99	99	16

*At time of beginning insulin treatment.

TABLE 23.—*Continued*

Case No.	Sex	Age*	Duration* of Diabetes	Diet						Height*		Body Weight, Lb.			Present Insulin Dosage, Units per Day
				Highest Without Insulin			Highest With Insulin								
				P. Gm.	C.H. Gm.	Cal.	P. Gm.	C.H. Gm.	Cal.			Before Diabetes	Before Insulin	After Insulin	
		Yrs.	Years							Ft.	In.				
1305	M	39	1½	...	...	....	100	128	2172	5	6	198	166	120	10
1306	M	9	2 mo.	70	55	2000	80	100	2400	4	4	62	58	65	10
1307	M	45	2½	...	...	....	60	30	1500	6	0	175	132	134	21
1308	M	41	1	70	40	1900	100	100	3000	6	0	170	104	120	36
1312	F	55	10	..	...	....	80	100	2500	5	1	165	125	126	14
1316	M	64	7	...	...	....	65	50	1800	5	3	162	113	113	15
1317	F	47	2½	...	...	....	80	120	2789	5	3	140	90	124	34
1319	F	1½	3 mo.	...	...	....	50	50	900	2	9½	27	20	25	12
1331	M	21	1½	...	...	....	100	75	2000	5	7½	120	92	99	20
1332	M	28	1	...	...	....	100	80	2300	5	7¼	127	109	114	33
1333	M	3	½	...	...	....	80	100	1500	3	4¾	40	39	41	12
1334	F	47	2½	...	...	....	80	80	2500	5	3	208	130	131	20
1344	F	40	2	...	...	....	80	80	1800	5	3	99	77	81	18
2071	M	50	1	60	25	1200	100	100	2400	5	9	175	118	130	18
2127	F	4½	9 mo.	...	...	....	70	65	1650	3	1	...	...	44½	12
2165	M	72	11	...	...	....	100	100	2426	5	4½	200	158	...	...
2186	F	30	3	...	...	....	40	15	600	5	2½	118	80	85	12
2215	F	34	1	...	...	....	100	100	2500	5	5⅜	145	97	101	20
2228	M	7	.....	55	40	1300	65	80	1700	3	1	50	45	45	6
2229	M	24	3 mo.	...	...	....	80	80	2000	5	11	156	126	131	21
2230	M	12	.....	80	50	1800	90	100	2400	5	1⅞	105	98	99	4
2232	F	34	1	...	...	....	70	60	1800	5	6	152	116	116	20
2243	M	5	2	...	...	....	65	55	1650	3	3½	...	28	35	18
2249	M	30	1	...	...	....	100	100	2400	5	10	149	116	126	18

*At time of beginning insulin treatment.

dangers which might be feared from hypoglycemia during sleep. Some carbohydrate may be saved from the regular diet and given with the midnight dose if necessary to prevent hypoglycemia. Further experience of ourselves or others may evolve some better plan. Up to the present, under our method of treatment, the tendency to morning hyperglycemia and evening hypoglycemia remains the chief difficulty with severe cases in general. On the whole it is successfully overcome by sufficiently accurate study of the adjustment between dosage and diet, and especially by avoiding attempts at overnutrition.

II. General Results of Insulin Treatment.

1. Statistical Summary:—A conspectus of the clinical changes accomplished with insulin in 87 cases, particularly as regards increases of diet and weight, is shown in Table 23. It is to be understood that the results in most cases are incomplete and improvement is still in progress.

2. Significance for Theory of Diabetes:—One interesting result is that all cases of diabetes have responded to insulin treatment. No refractory case has yet been found, and the variations in dosage required are mostly explainable by the severity and other definite factors and in no case have seemed to require the assumption of any extra-pancreatic cause of the diabetes. None of the first group of workers with insulin have doubted that pancreatic disease is the sole origin of diabetes, but the widespread use of the new treatment will probably assure the widespread acceptance of this view. It is hard to understand the vagaries of medical and scientific opinion; for example, why so many persons should have doubted this doctrine, which was already as well proved as most doctrines in physiology or pathology, and why so many should have accepted a theory which never had any real evidence in its favor, namely, that of the alleged participation of the adrenals and other glands in the etiology of diabetes. The unity of diabetes is now further established, and diabetes is scientifically definable only as deficiency of the internal secretion of the pancreas.

3. Immediate Effects Upon Blood and Urine Sugar:—Tests were made at the beginning with small doses of insulin controlled by frequent blood and urine analyses, sometimes in comparison with saline injections to exclude psychic influence. Some of the

results are shown in tables 24 to 30. It is to be understood that the patients received their regular meals at 8 A. M., noon, and 5 P. M. It is remarkable that fractions of a unit of insulin should have produced evident results in reducing the urinary and blood sugar in severe cases of diabetes, so that the tendency toward a rise after meals was converted into an actual fall. The control days with saline injections prove that the effect was real. Still more remarkable is the hypoglycemic collapse with profound unconsciousness in an adult man with severe diabetes (No. 1194) when the total dosage on the preceding days had been only 1 unit

TABLE 24

Case No. 54

Date 1922	Hour	Diet			Plasma Sugar Mg. Per 100 cc.	Urine		Insulin, Units
		P. Gm.	C.H. Gm.	Total Cal.		Glucose	Nitro-prusside	
Aug. 10	8.00 a.m.	16	2	400	349	0	0	⅓
	9.00	..	..	...	319	....	....	...
	10.00	..	..	...	260	....	....	...
	11.00	..	..	...	270	....	....	...
	12.00	16	2	400	...	0	....	...
	5.00 p.m.	16	2	400	...	0	....	...
11	8.00 a.m.	16	2	400	246	+	....	½
	9.00	..	..	...	255	....	....	...
	10.00	..	..	...	230	....	....	...
	11.00	..	..	...	221	....	....	...
	12.00	16	2	400	...	....	....	...
	5.00 p.m.	16	2	400	...	....	....	0
12	8.00 a.m.	16	2	400	255	+	....	...
	9.00	..	..	...	319	....	....	...
	10.00	..	..	...	319	....	....	...
	11.00	..	..	...	319	....	....	...
	12.00	16	2	400	...	+	....	...
	5.00 p.m.	16	2	400	...	+	....	...
15	8.00 a.m.	16	2	400	275	0	....	1
	11.00	..	..	...	280	....	....	..
	12.00	16	2	400	...	0	....	1
	3.00 p.m.	..	..	...	168	....	....	...
	5.00	16	2	400	...	....	....	1
	8.00	..	..	...	136	0	....	...
16	8.00 a.m.	16	2	400	223	0	....	1
	12.00	16	2	400	...	0	....	1
	3.00 p.m.	..	..	...	139	....	....	...
	5.00	16	2	400	...	....	....	1
	8.00	..	..	...	156	0	....	...

TABLE 25

Case No. 574

Date 1922	Hour	Diet				Plasma Sugar	Urine		Insulin, Units
		P. Gm.	F. Gm.	C.H. Gm.	Total Cal.	Mg. Per 100 cc.	Glucose	Nitroprusside	
Aug. 17	8.00 a.m.	20	20	2	268	117	0	+	2
	11.00	..	..	..	...	93	0	0	
	12.00	20	20	2	268	..	...	.	.
	3.00 p.m.	..	..	..	..	93	0	0	
	5.00	20	20	2	268	...	....	.	.
18	8.00 a.m.	20	20	2	268	—	....	0	0
	12.00	20	20	2	268	...	....	.	.
	5.00 p.m.	20	20	2	268	...	....	..	
	8.00	..	..	..	...	319	....	..	
21	8.00 a.m.	20	20	2	268	441	++++	..	0
	12.00	20	20	2	268	..	++	..	
	5.00 p.m.	20	20	2	268	...	....	..	.
	8.00	..	..	..	...	441	++++	..	..
22	8.00 a.m.	20	20	2	268	230	++++	..	½
	12.00	20	20	2	268	...	0	..	.
	3.00 p.m.	..	..	..	...	385	....	..	..
	5.00	20	20	2	268	...	....	..	½
	8.00	..	..	..	...	357	++	..	.
23	8.00 a.m.	20	20	2	268	238	++	..	1
	12.00	20	20	2	268	...	0	..	..
	3.00 p.m.	..	..	..	..	141	....	..	...
	5.00	20	20	2	268	...	++	..	1

and the injection which precipitated the crisis was of only half a unit. On higher diets such a case could not have been influenced in such a manner by such doses. It and others of the sort illustrate strikingly the benefits of extreme undernutrition in reducing the insulin requirement to a minimum when the most extreme sparing of the internal pancreatic function is necessary. This patient was emaciated to a point where evidently his food reserves were nearly exhausted. The remarkable effect of a trivial dose of insulin aids in the disproof of any speculative assumptions that in such a state of inanition the body is forming sugar from its own protein to such an extent as to place a heavy burden upon the insular function (cf. paper 3). When the nutritive condition was better (case 1073) or the diets higher (cases 574 and 1034) larger doses were required for sugar-freedom.

TABLE 26

Case No. 1034

Date 1922	Hour	Diet			Plasma Sugar Mg. Per 100 cc.	Urine			Insulin, Units
		P. Gm.	C.H. Gm.	Total Cal.		Vol. cc.	Glucose, %	Nitroprusside	
Aug. 10	8.00 a.m.	20	2	268	....	....	....	....	....
	12.00	20	2	268	577	695	1.26	....	⅓
	1.00 p.m.	..	..	....	565	121	1.26	....	....
	2.00	..	..	....	510	420	.42	....	⅓
	3.00	..	..	....	500	102	++++	....	....
	4.00	..	..	....	555	....	++++	....	....
	5.00	20	2	268	....	....	....	....	....
11	8.00 a.m.	20	2	268	577	....	++++	....	½
	9.00	..	..	....	455	....	++++	....	....
	10.00	..	..	....	469	....	++++	....	....
	11.00	..	..	....	441	....	++++	....	....
	12.00	20	2	268	....	....	....	....	....
	5 p.m.	20	2	268	....	....	....	....	....
12	8.00 a.m.	20	2	268	518	....	++++	++	½
	9.00	..	..	....	555	270	.80	++	....
	10.00	..	..	....	484	505	.74	++	1
	11.00	..	..	....	484	65	1.63	++	....
	12.00	20	2	268	405	240	.38	++	....
	1.00 p.m.	..	..	....	....	205	0	0	1
	2.00	..	..	....	326	205	0	0	....
	3.00	..	..	....	285	200	0	0	....
	4.30	..	..	....	230	100	0	0	2
	5.00	..	..	....	....	145	0	0	....
	6.00	20	2	268	....	10	0	0	....
	7.00	..	..	....	....	245	0	0	....
	8.00	..	..	....	138	280	0	0	....
13	8.00 a.m.	20	2	268	385	....	++++	....	....
	8.30	..	..	....	....	....	....	....	2
	9.00	..	..	....	....	91	1.54	++	....
	10.00	..	..	....	....	168	.90	++	....
	11.00	..	..	....	....	210	.65	++	....
	12.00	20	2	268	319	82	.60	++	2
	1.00 p.m.	..	..	....	....	110	.13	++	....
	2.00	..	..	....	....	260	0	0	....
	3.00	..	..	....	....	440	0	0	....
	5.15	20	2	268	....	130	0	0	2
	9.00	..	..	....	143	280	0	0	....
	12.00 m.	..	..	....	....	50	....	....	2
14	8.00 a.m.	20	2	268	220	110	0	+	2
	12.15 p.m.	20	2	268	189	....	0	0	2
	3.00	..	..	....	117	....	0	0	....
	5.30	20	2	268	....	....	0	0	2
	8.30	..	..	....	126	....	0	0	....
	11.15	..	..	....	....	....	....	....	2
15	8.00 a.m.	20	2	268	91	....	0	0	2
	12.00	20	2	268	80	....	0	0	2
	5.00 p.m.	20	2	268	85	....	0	0	2
	12.00 m.	..	..	....	....	....	0	0	1
16	8.00 a.m.	20	2	268	180	....	0	0	1
	12.00	20	2	268	95	....	0	0	1
	5.00 p.m.	20	2	268	132	....	0	0	1
	12.00 m.	..	..	....	....	....	0	0	1

4. Results in Cases Under Long Observation:—Any accidental element in the benefits observed, due perhaps to spontaneous fluctuations of tolerance, can be best excluded by the observations of cases in which the tolerance has been accurately fixed throughout a number of years. For example, certain patients (e.g. Nos. 24, 54, 85, 839, 878, 1034, 1073) have lived continuously in this

TABLE 27

Case No. 1044

Date 1922	Hour	Diet				Plasma Sugar Mg. Per 100 cc.	Urine		Insulin, Units
		P. Gm.	F. Gm.	C.H. Gm.	Total Cal.		Glucose	Nitroprusside	
Aug.									
9	.....	35	23	..	350	255	0	..	..
10	8.00 a.m.	12	7	..	111	270	0	..	1/3
	9.00	..	..	..	...	263	0	..	...
	10.00	..	..	..	...	226	0	..	...
	11.00	..	..	..	...	238	0	..	..
	12.00	12	8	..	120	...	..	..	..
	5.00 p.m.	12	8	..	120	...	..	..	..
11	8.00 a.m.	12	7	..	111	246	0	..	1/2
	9.00	..	..	..	...	265	0	..	..
	10.00	..	..	..	...	234	0	..	..
	11.00	..	..	..	...	230	0	..	..
	12.00	12	8	..	120	..	..	..	..
	5.00 p.m.	12	8	..	120	...	..	..	..
12	8.00 a.m.	12	7	..	111	275	0	..	0
	9.00	..	..	..	...	285	0	..	...
	10.00	..	..	..	...	275	0	..	..
	11.00	..	..	..	...	290	0	..	..
	12.00	12	8	..	120	..	..	..	..
	5.00 p.m.	12	8	..	120	...	..	..	..
13	.....	35	23	..	350	—	0	..	0
14	8.00 a.m.	12	7	..	111	—	0	..	0
	12.00	12	8	..	120	...	..	..	..
	3.00 p.m.	..	..	..	...	290	0	..	
	5.00	12	8	..	120	....	..	..	
	8.00	..	..	..	...	283	0	..	..
15	8.00 a.m.	12	7	..	111	300	+	..	1
	12.00	12	8	..	120	..	..	..	1
	3.00 p.m.	..	..	..	...	125	0	..	
	5.00	12	8	..	120	..	..	..	1
	8.00	..	..	..	...	131	0	..	..
16	8.00 a.m.	12	7	..	111	223	0	..	1
	12.00	12	8	..	120	...	..	..	1
	3.00 p.m.	..	..	..	...	150	0	..	
	5.00	12	8	..	120	..	..	..	1
	8.00	..	..	..	.	153	0	..	..

Institute for periods between one and four years. Others (e.g. Nos. 2, 3, 174, 191, 337, 539, 574, 783) have been under exact care and observation at home for periods extending as far back as 1914. These cases and others like them have been used heretofore for the demonstration that diabetics do not necessarily progress downward when functional injuries are avoided. On the other hand, gain of tolerance in severe cases of this character is absent or trivial. When, therefore, patients of this type are enabled to

TABLE 28

Case No. 918

Date 1922	Hour	Diet			Plasma Sugar Mg. Per 100 cc.	Urine		Insulin, Units
		P. Gm.	C.H. Gm.	Total Cal.		Glucose	Nitro-prusside	
Aug. 10	8.00 a.m.	5	1	100	...	0	0	...
	10.00	5	..	...	300	....	....	...
	11.00	..	..	...	260	0	....	⅓
	12.00	5	1	100	189	0	0	...
	1.00 p.m.	..	..	...	184	0	....	...
	5.00	5	1	100	...	....	....	..
11	8.00 a.m.	5	1	100	290	0	0	½
	9.00	..	..	...	265	0	....	...
	10.00	..	..	...	246	0	...	...
	11.00	..	..	...	209	0	...	...
	12.00	5	1	100	...	....	....	...
	5.00 p.m.	5	1	100	..	....	....	...
12	8.00 a.m.	5	1	100	366	0	0	½
	9.00	..	..	...	...	....	....	...
	10.00	..	..	...	319	....	....	1
	11.00	..	..	...	223	....	....	...
	12.00	5	1	100	..	....	....	...
	2.00 p.m.	..	..	...	74	....	....	2
	3.00	..	..	...	53	....	....	...
	4.00	..	..	...	52	....	....	2
	5.00	5	1	100	...	....	....	...
	7.00	..	..	...	68	....	....	..
13	8.30 a.m.	5	1	100	...	0	0	...
	8.45	..	..	...	94	....	....	2
	12.15	8	2	133	...	....	....	...
	1.15 p.m.	..	..	...	51	....	....	...
	2.30	..	..	...	...	....	....	1
	5.15	8	1	133	...	....	....	1
	9.00	..	..	...	39	....	....	...
15	8.00 a.m.	10	3	166	...	0	0	1
	12.00	10	3	166	...	....	....	1
	4.00 p.m.	..	..	..	59	....	....	...
	5.30	10	3	166	...	....	....	1

assimilate greatly increased diets and to gain weight and strength in an unexampled manner, these benefits must be attributed strictly to insulin.

TABLE 29

Case No. 1073

Date 1922	Hour	Diet			Plasma Sugar Mg. Per 100 cc.	Urine			Insulin, Units
		P. Gm.	C.H. Gm.	Total Cal.		Vol. cc.	Glucose, %	Nitro-prusside	
Aug. 10	8.00 a.m.	10	..	...	...	....	...	....	..
	11.00	..	..	...	405	...	+++	0	1/3
	12.00	10	..	...	395	218	.52	0	...
	1.00 p.m.	..	..	...	326	265	.27	0	...
	2.00	..	..	...	357	250	.21	0	..
	5.00	10	..	...	....	....	....	....	...
11	8.00 a.m.	10	..	...	319	....	++++	0	1/2
	9.00	..	..	...	280	....	++	0	...
	10.00	..	..	...	209	....	0	0	...
	11.00	..	..	...	211	....	0	0	..
	12.00	10	..	...	...	..	.	...	..
	5.00 p.m.	10	..	...	...	....	....	....	...
12	8.00 a.m.	10	..	...	295	....	0	0	0
	9.00	..	..	...	319	....	0	0	..
	10.00	..	..	...	294	....	0	0	...
	12.00	10	..	...	312	....	+	....	
	5.00 p.m.	10	..	...	...	....	....	...	.
14	8.00 a.m.	10	..	..	...	....	0	0	0
	12.00	10	..	...	...	....	0	0	..
	5.00 p.m.	10	..	...	306	....	0	0	...
	8.00	..	..	...	319	....	+++	0	..
15	7.55 a.m.	10	..	...	349	....	+++	0	1
	11.15	..	..	...	...	..	....	....	1
	12.15 p.m.	10	..	...	...	..	0	0	..
	3.30	..	..	...	164	.	....	....	...
	5.15	10	..	...	..	.	0	0	1
	8.30	..	.	...	119	...	.	...	..
16	8.00 a.m.	10	..	...	242	....	0	+	1
	12.30 p.m.	10	..	...	..	.	0	0	1
	3.00	..	..	...	139	..	....	.	
	5.30	10	..	...	...	.	0	+	1
	8.00	..	..	...	115	....	...	.	
17	8.00 a.m.	10	..	...	157	....	0	0	1/2
	12.15 p.m.	10	..	...	..	...	0	0	..
	3.00	..	..	...	214		.	.	
	5.15	10	..	...	...	.	0	0	1/2
	8.00	..	..	...	209	..	.	..	.

TABLE 30

Case No. 1194

Date 1922	Hour	Diet			Plasma Sugar Mg. Per 100 cc.	Urine			Insulin, Units
		P. Gm.	C.H. Gm.	Total Cal.		Vol. cc.	Glucose, %	Nitro-prusside	
Aug. 10	8 a.m.	7	2	...	....	..	....	....	...
	11.00	..	..	...	536	..	++++	++	½
	12.00	..	..	...	500	110	1 1	....	...
	12.15 p.m.	7	2	...	....	..	....	....	...
	1.00	..	..	...	429	17	1 2	....	...
	2.00	..	..	...	484	90	.3	....	...
	5.00	7	2	...	....	..	....	....	...
11	8.00 a.m.	7	2	...	429	..	+	0	½
	9.00	..	..	...	469	..	....	....	...
	10.00	..	..	...	455	..	....	....	...
	11.00	..	..	...	455	..	....	....	...
	12.00	7	2	...	....	..	0	0	...
	5.00 p.m.	7	2	...	....	..	....	....	...
12	8.00 a.m.	7	2	...	469	..	0	0	0
	9.00	..	..	...	469	..	....	....	...
	10.00	..	..	...	500	..	....	....	...
	11.00	..	..	...	518	..	+	+	...
	12.00	7	2	...	....	..	....	....	...
	5.00 p.m.	7	2	...	....	..	....	....	...
15	8.00 a.m.	7	2	...	416	..	0	0	1
	12.15	7	2	...	..	..	0	0	1
	3.30	..	..	...	242	..	0	0	...
	5.15	7	2	...	..	..	....	....	1
	8.40	..	..	...	129	..	....	....	...
16	8.00 a.m.	7	2	...	164	..	0	0	1
	12.30 p.m.	7	2	...	....	..	0	0	1
	3.00	..	..	...	106	..	....	....	...
	5.30	7	2	...	....	..	....	....	1
	8.00	..	..	...	115	..	....	....	...
17	8.00 a.m.	7	2	...	116	..	0	0	½
	12.30 p.m.	7	2	...	....	..	....	....	...
	3.30	..	..	...	146	..	0	0	½
	5.30	7	2	...	....	..	....	....	...
	8.00	..	..	...	109	..	0	0	...
20	8.00 a.m.	7	8	...	077	..	0	0	½
	12.15 p.m.	7	8	...	....	..	0	0	...
	3.00	..	..	...	091	..	....	....	½
	5.15	7	8	...	....	..	0	0	...
	8.06	..	..	...	061	..	....	....	...
22	8.00 a.m.	7	13	...	....	..	0	0	½
	12.15 p.m.	7	13	...	....	..	....	....	...
	3.00	..	..	...	069	..	0	0	...
	5.15	7	13	...	....	..	....	....	½
	8.00	..	..	...	053	..	0	0	...
	8.35	..	25	...	....	..	....	....	...
	9.05	..	40	...	....	..	....	....	...
	10.00	..	..	...	....	..	+++	....	...

TABLE 30—*Continued*

Date 1922	Hour	Diet			Plasma Sugar Mg. Per 100 cc.	Urine		Insulin, Units
		P. Gm.	C.H. Gm.	Total Cal.		Glucose, %	Nitroprusside	
Aug. 23	8.00 a.m.	8	15	..	046	0	0	$^1/_2$
	10.45	..	..	..	042	....	....	..
	11.00	..	40	..	.	....	....	..
	12.00	10	5	400	..	0	0	..
	1.00 p.m.	..	..	....	057	....	....	..
	1.15	10	14	260	..	....	....	..
	2.15	15	10	582	076	....	....	..
	5.15	50	70	900	....	0	0	..
	6.15	..	..	..	150	++	0	..

5. Results in Extremely Severe Cases:—Some cases (e.g. Nos. 918, 1034, 1054, 1212, 1214, 2186) have been found of such unusual severity that the saving of life by diet treatment alone was clearly impossible. The records of a large proportion of our entire series of cases will show that they are decidedly severe, because preference has been given to severe cases in the use of insulin. By unaided diet treatment it has been possible to keep these patients alive, often over long periods of years as already mentioned, but only at the price of privation, emaciation and weakness in proportion to the severity of the disease. To these patients insulin has meant that they might not merely have life, but have it more abundantly. The recovery of weight and vigor after such prolonged and extreme undernutrition has been an interesting process. A further answer is thus provided to one former doubt or criticism, namely, that the extreme undernutrition in these cases might be unnecessary or might even serve to reduce the food tolerance. Just as it was formerly proved that reductions of total calories and body weight raised the tolerance, even when carried to an extreme degree in extremely severe cases, so now it has been demonstrable that every increase of the diet with any kind of food has required an increase of insulin dosage in these patients. The increases of diet have seldom been given suddenly, even since the supply of insulin has become adequate, and it has been considered best to allow these patients to come back gradually to health and strength on a caloric allowance within approximately normal limits, with insulin dosage carefully adjusted to keep symptoms under control, except when experimental conditions required temporary departures from this rule. The

most gratifying result is that these patients, in all degrees of emaciation and severity of diabetes, are apparently able to recover satisfactorily with the aid of insulin, and only sufficient food and sufficient time seem necessary to enable them to resume an approximately normal mode of life, including self-support. The number of helpless invalids in hospitals or homes is thus appreciably reduced, and the typical emaciated diabetics of the past will disappear.

6. *Results in Moderate or Mild Cases:*—Patients with the mildest diabetes should seldom receive insulin, partly because they will not wish to be troubled long with the subcutaneous injections if they can tolerate a satisfying diet without them, and partly because they do not need to undergo any possible remote risks connected with a powerful new drug. A distinct exception is presented by youthful patients with incipient diabetes, for which the use of small doses of insulin in connection with accurate diet is probably of the highest prophylatic importance. A numerous class of diabetics remain (e.g. cases No. 274, 314, 339, 1126 and others) whose privations have not been extreme, but nevertheless have been sufficient to cause some retardation of development in children and some impairment of looks, comfort and earning capacity in adults. The exact level to which the nutrition of these patients should be raised by the use of insulin remains somewhat uncertain, but there is no doubt that moderate doses result in great improvement and that many patients can thus be restored to fuller vigor and earning capacity. In addition, there are occasional patients whose diabetes may be mild but is attended by disproportionate weakness, depression, neurosis or other symptoms (e.g. cases 396, 1312, 1334). In these cases the use of moderate doses of insulin may give benefits which are not psychic but due to the improved nutrition. In all the above classes of cases, from the severest to the most moderate type, the insulin treatment carries not only a great increase of personal happiness but also a distinct economic gain to the patients, their families and the community.

7. *Results in Terms of Tolerance for Different Foodstuffs:*—The case records will show that, except for experimental purposes, we have not used seriously one-sided diets. The experiments described in papers 2 and 3 show that fat, protein and carbohydrate constitute an ascending series in respect to the

insulin requirement created when an equal number of calories is given in these respective forms. The relations are such as have already become familiar through dietary studies. Any alleged injuriousness of protein, because of specific dynamic action or unknown toxic effects, is discredited by the experiments. The differences between fat and carbohydrate are greatest in the shortest tests, and in the long run are not sufficient to warrant the inconvenience and discomfort, if not actual danger, of an overbalanced fat ration. No fixed rules of protein requirement or ketogenic-antiketogenic balance have been followed. The principle has merely been to give a thoroughly safe sufficiency of both protein and carbohydrate while avoiding excesses. Thus, for a diet of 2000 calories, we have commonly allowed 100 gm. protein and 100 to 150 gm. carbohydrate. The difference in insulin requirement as compared with a diet composed more largely of fat is relatively slight in the long run, while there are very important differences in comfort, in the ability to eat at least limited quantities of most articles of a normal diet, and in freedom from acidosis dangers.

8. Results in Terms of Total Diet and Body Weight:—Our objections to arbitrary rules and preference for individualization apply also in these matters. Undoubtedly a smooth course of treatment is best assured by undernutrition of sufficient degree to keep the insulin dosage within very moderate bounds. With higher nutrition and higher dosage, the difficulties of avoiding hypoglycemia on the one hand and glycosuria and other diabetic symptoms on the other are progressively increased. At the same time, the demands for growth and development in children and for well-being and working capacity in adults require consideration. We have tried to supply these needs, using for the purpose somewhat higher average insulin dosage than Joslin, for example, but at the same time we share his views against overnutrition and agree with him on the advisability of keeping most diabetics at least a few pounds below the average normal weight for their height. We are opposed to any avoidable undernutrition, and believe that normal persons are better off for the liberal diets which they generally consume. Undernutrition is most unfortunate in children, but at the same time diabetes is most dangerous in them, and past experience has proved that when a choice is necessary it is better to take strict care of the diabetes at any

sacrifice of nutrition. The plan of treatment in individual cases must be adjusted not only to personal or ideal requirements but also to social and financial conditions. Patients who are unable to pay for much insulin must reduce their need for it by stricter undernutrition. If a higher diet raises the earning capacity sufficiently, a higher dosage of insulin may be a good investment even for a day laborer. Relying for guidance upon laboratory tests, especially blood analyses, we have felt justified in permitting more liberal nutrition in proportion as the individual environment permitted more accurate control. The sharpest contrast in this respect is furnished by cases 989 and 1034, which are discussed in paper No. 3 for their experimental value. The girl, No. 989, has clearly a less severe diabetes than the boy, No. 1034, yet she has received 70 insulin units daily as opposed to his 8 units, merely because her diet is so much higher. The boy has been cheerful, active, not hungry, and at the same time freer from hypoglycemia, glycosuria, acidosis and all kinds of ups and downs than the girl. On the other hand, he is thin and altogether subnormal physically, and has made no gain in height, while she is the picture of beautiful health and exuberant spirits and is growing rapidly. The boy is highly intelligent and trustworthy, but he has been treated on a charity basis and must largely carry the responsibility of his own treatment at home. Diet and dosage as high as in the girl's case would quickly bring disaster to him in spite of his efforts. The girl's family are wealthy and intend, no matter what treatment is followed, to keep a highly skilled nurse in charge indefinitely. The close care of this nurse guards against accidents and apparently makes safe an abundant nutrition which is gratifying to the child and her family. Her chances for growth and development are much brighter by reason of her more advantageous environment, but on the other hand it will be noticed that the boy has apparently shown the greater gain in tolerance. These two cases are to be regarded as extreme and exceptional. The girl's diet will be reduced unless she loses adipose tissue and gains height and muscle with increased exercise at home, as anticipated. The boy's diet will be raised to a moderate extent. Most cases will be treated on an intermediate basis, with smaller adjustments to individual circumstances. We hope frankly to learn by further experience which method is best and toward which side it is generally safer to lean.

9. Results in Relation to Exercise:—It is obvious that a diabetic supporting himself by manual labor requires extra food to cover the expenditure of muscular energy. Former investigations have shown that the increased metabolism of work does not impair tolerance but on the contrary improves the assimilation of food, at least in cases not of extreme severity. Important questions remain unanswered by these incomplete researches, and experiments with insulin will doubtless throw more light on the subject. Does exercise stimulate the pancreatic islands to an increased production of internal secretion? Does it enable the body cells to make more efficient use of the same insulin supply? Does the combustion of carbohydrate by exercise use up the same amount of insulin as the utilization of the same carbohydrate without exercise, and will hard exercise increase or diminish the tendency to hypoglycemia with a given dose of insulin? Does carbohydrate burned in exercise combat acidosis to the same extent as the same amount of carbohydrate utilized without exercise? The former experiments,[10, 11] though not fully conclusive, created the impression that exercise acts chiefly as a form of undernutrition. With the identical diet, there seems to be less strain upon the internal pancreatic function if food materials are burned up by exercise than if they are allowed to accumulate in the body. The results when an increase of food is given exactly balancing the increased consumption by exercise are uncertain. Habitual exercise results not only in increased energy output during the work but also in raising the basal metabolism. The consumption of insulin in the body undoubtedly rises and falls in large measure with the total metabolism; nevertheless it is improbable that this parallelism is uniform, or in other words that the insulin consumption is necessarily increased by elevations of metabolism in general or by the form of increase resulting from muscular labor in particular. The experiments performed on patients 191, 787 and 989 indicate similar effects of exercise under insulin treatment as formerly under diet treatment. The utilization of sugar seems to be facilitated and the tendency to hyperglycemia diminished. This influence is slight, and the impression may be created that it is less with insulin treatment than without insulin. Such a result may perhaps be due only to the higher level of diet, in both carbohydrate and total calories, as compared with cases formerly tested without insulin, or it may possibly suggest that in mild or moderate diabetes, when the

islands are able to respond fairly well to functional stimuli, exercise may call forth an actual increase of insulin production. The one important practical point learned from these tests is that heavy exercise increases the tendency to hypoglycemia, so that it may be necessary to warn against sudden overexertion in some cases.

10. Results in Relation to Other Metabolic Disorders:—In case No. 24, which is complicated with nephritis, the treatment of the diabetes with insulin seems to have had a slightly beneficial effect upon the renal function, probably due to the stronger circulation connected with the improved nutrition. In two other cases of renal disease, one with hypertension and the other of the "nephrosis" type, trials of insulin for a few days seemed negative. A similar brief test in a neurotic patient, without diabetes but with poor strength and nutrition, seemed to show no special tonic or invigorating properties of insulin. It is conceivable that chronically thin persons without known disease may have their appetite and nutrition improved by suitable use of insulin, but such a suggestion is purely speculative. On the whole, insulin seems to be a specific for diabetes, and is likely to be disappointing to the persons who explain all sorts of ailments by deficiencies and imbalances of glands.

Caution may be necessary, however, against an equally extreme opposite position, which may unduly disregard the possible influence of hormonal excess upon the body in general or upon other glands. The following observations may be suggestive. One very noticeable early effect of insulin treatment is a filling out of the face which may become noticeable within a day or two or even within a few hours after the first dose of insulin. This fullness of the face persists, and certainly in the early stage and possibly also in later stages of the treatment it is out of proportion to the general gain of weight. The skin is generally noticeably clear. The patients seem to tend readily to become obese, and it is questionable if there is not an undue proportion of fat deposited on the trunk in comparison with the limbs. The general appearance of patients who have thus been unduly fattened with insulin is more or less suggestive of the so-called dystrophia adiposo-genitalis. With proper insulin dosage and diet, adults undoubtedly recover normal musculature and strength, and children grow and develop well. Only one girl (No. 1065) has had a

return of menstruation under insulin treatment. The continued absence of it in patients, such as No. 3, who have been nourished even to the point of obesity, is somewhat surprising. It will be a matter of interest to note the return of menstrual function in the cases in which it has been suppressed through many years of severe diabetes, and its delay may possibly be explained merely by organic changes during the interval. From every standpoint, however, physicians should be on their guard against the possible consequences of flooding the body with one of its most powerful hormones.

11. Influence on Fidelity:—All patients who received treatment with insulin at first were of the scrupulously faithful type. As the supply of insulin became more liberal, trials were made to learn how the habitually unfaithful type of patients would react to the new treatment. It is possible to adopt an inflexible attitude and declare that only trustworthy patients deserve the benefits of insulin and that there is too much danger in giving it to the other kind. In actual practice, however, a considerable proportion of diabetics are of a more or less careless and untrustworthy type. Such patients have always been given the opportunities of diet treatment, and are dismissed from supervision only after proving themselves incorrigible. With a sufficient supply of insulin, it is inevitable under medical practice and ethics that all patients shall receive the opportunity of the increased benefit. The necessity of subcutaneous injections two or more times daily, together with an accurate diet, imposes a greater burden than before, but on the other hand the higher diet thus made possible removes one of the chief temptations.

Greatly improved morale and fidelity, due to better diet and greater hope, have been noted in cases No. 3, 179, 216, 328, 356, 518, 526, 833, 1073, 1083, 1156 and 1194. The chances for success in unfavorable environment seem also brighter in such a case as No. 2228. On the other hand, gross disregard of treatment continued in cases No. 356, 1044, 1062 and 1277. The outcome in No. 1062 and No. 1277 was fatal, and the prognosis must be considered poor in the other two. Now, just as with the former diet treatment, fidelity cannot be predicted from any criteria of intelligence or social position. The reasonable demands of patients for comfort and strength can be supplied, but there is still no remedy for weak will and indulgence of appetite. Our general

experience indicates that the average of fidelity is greatly raised by insulin treatment.

12. Abuses of Insulin:—The use of insulin to fatten patients unduly or to enable an obese diabetic to remain obese, or for gratifying mere gluttony or craving for excessive sugar and starch, or for avoidance of the inconvenience of an accurately weighed diet on the part of the patient or physician, must be considered inexcusable and dangerous. These forms of misuse are to be anticipated on a large scale when insulin becomes generally available, and furthermore will probably be hard to combat because the harm may not be immediately evident. The danger of sudden acidosis from irregularities of treatment in over-fed diabetics should be borne in mind. Strong warnings should therefore be given against such practices, until time shall bring a general understanding that good and bad results are determined not merely by insulin but fully as much by the manner in which insulin is used.

III. Treatment of Diabetic Coma.

1. Statistical Results:—We have used insulin in the treatment of 9 coma cases, with 4 recoveries (Nos. 1214, 1317, 1346, 2249) and 5 deaths (Nos. 1296, 1302, 1321, 1348, 1366). The degree of success shown in such records will be governed largely by the degree of acidosis to which the term coma is applied. All criteria for prognosis are superficial and undependable. The quantitative acetone figures in blood and urine apparently mean little for comparisons between cases. The CO_2 capacity of the blood plasma is influenced largely by alkali administration and other factors, and at best is not a measure of the fundamental process which causes death. The clinical signs of dyspnea and stupor are highly important guides, but patients showing them in the highest degree sometimes recover while those in a seemingly less advanced condition sometimes die. Patients in the stage of profound unconsciousness formerly died practically without exception. With insulin treatment the majority of them still die but an appreciable number are saved. With lesser grades of acidosis the results are much better. It is improbable that more than one (No. 2249) of the 9 patients in this list could have survived without insulin. The demonstration of benefit is particularly clear in a case such as No. 1317, when the coma which is cleared up by insulin

threatens to return when insulin is omitted. The saving of lives in the emergencies of acidosis is rightly hailed as one of the strongest proofs of the specific value of insulin for diabetes. The fact still remains that diabetic coma is generally avoidable and that the death rate can be reduced far more by early prevention than by attempts at last-minute cures.

2. *Auxiliary Measures:*—The fact should not be lost sight of that the great majority of cases in which coma is impending but not yet present can be treated successfully without insulin, as our records and those of Joslin abundantly show. Withdrawal of all food except the carbohydrate represented in the juice of citrus fruits (from a pint to a quart of which may be given in 24 hours), as much fluid as possible (5 to 10 quarts in 24 hours, by mouth if possible, or in the form of saline solution by rectum, intravenously or subcutaneously if necessary), purgation or high enemas, and sodium bicarbonate in 5-gram doses by mouth up to 20 to 50 gm. in 24 hours (rarely in small doses intravenously) will still generally serve the purpose if insulin is not available, and should be used also as adjuvants in cases in which insulin is given. Two changes are advisable in the latter cases; first, sodium bicarbonate should generally be used in somewhat smaller quantities, in order to avoid the danger of alkalosis following the rapid disappearance of acids (this danger being greatest if diuresis is slight), and second, more sugar than advised above should be given when the insulin dosage is very high. Quickly assimilable sugar for this purpose may be given in such forms as grape juice, honey, the syrupy glucose of confectioners, or Karo corn syrup, for patients who can swallow and absorb, while pure glucose in 5 per cent. or stronger concentrations in saline solution may be given intravenously to unconscious patients. Probably no harm is done if the total sugar administration runs between 100 and 300 gm. per day, though excesses should be avoided if the hyperglycemia and glycosuria are found to remain very high. There are two reasons for using sugar liberally with insulin and not depending on the supply which seems to be already superabundant in the body; first, as a safeguard against hypoglycemia and a means for using the highest possible insulin dosage without this danger; second, as a direct aid in combating the acidosis, since, under the "paradoxical law" of glucose, the more of it is given the more of it will be utilized with a fixed

insulin supply, and the utilization of glucose is the essential prerequisite for the combustion of the acetone bodies. The surplus sugar assists further by stimulating diuresis if the kidneys are still able to respond to the stimulus. This advice is practically identical with that already given by the Toronto investigators, who are fully justified in their view that the harmfulness of carbohydrate excess for a day or two is negligible in an emergency of this kind.

3. Insulin Dosage.—In the presence of actual or threatened coma, all ordinary limits of insulin dosage must be discarded and heroic doses used from the earliest possible moment. Our present custom, when called to a coma case, is to take a blood sample immediately and inject 25 units of insulin into the vein before the needle is withdrawn. An additional dose of 25 to 50 units is then immediately given subcutaneously. Further subcutaneous doses of 25 to 50 units are then given one to several hours apart, with no fixed rules but under the general guidance of both laboratory and clinical indications. It may perhaps be said that the purpose of sugar and insulin administration is to keep the blood sugar above 0.3 per cent. while clearing up acetone as quickly as possible. The safe or advisable limits of insulin dosage are unknown. The lowest and most conservative limit is doubtless the minimum quantity giving the desired results, which is seldom below 100 units in a dangerous coma case, unless undernutrition or other special factors have modified conditions. Whether any fixed number of units can be set as an upper limit, beyond which any increase of dosage is useless, and whether insulin in some huge amount may prove toxic even though the blood sugar be kept artificially elevated, are questions without any answers at present. The latter possibility is not wholly excluded in case 1348, in which we used 485 units of insulin, or in case 1321, in which we gave 270 units. Doses of 185 units in case 1317 and 335 units in case 1346 within 24 hours seemed to be not only harmless but also essential to success. Possible reasons for these extraordinary insulin requirements with heavy acidosis are so purely speculative at present that they are scarcely worth mention. In view of such requirements, there must be surprise not that patients in coma have generally died under the former treatment, but that so many of those with grave acidosis have been saved by dietary methods even when the severity of the

diabetes demonstrated that the pancreatic function was very small.

4. Autopsy Findings:—A fresh autopsy was obtained in one case (No. 1321) of coma treated with insulin. The findings differed from those familiar in severe diabetes in only two respects. (a) Hydropic changes in the pancreatic islands were so rare and slight that they were discovered only by long search. In view of the insulin requirements, as revealed by the above mentioned therapeutic observations, it is now easy to understand the intensity of the functional stimulation which drives these cells to the state of exhaustion represented by the hydropic pictures in most coma cases heretofore. The relative absence of such changes under insulin treatment is suggestive, but requires confirmation before any theoretical application is made. If infection be assumed as the chief cause of death, there is a previous observation[15] of almost as slight vacuolation of island cells in a case of diabetes with carbuncle, apparently explainable by the fact that the terminal severe stage of the previously mild diabetes was too short for the production of advanced hydropic degeneration, which requires at least several days. (b) The ulceration of a segment of intestine and the leukocytic infiltration of the pancreas are best explained as infectious, and any supposition that they were due to toxicity of the large insulin dosage must be highly improbable. No suspicion of infection, other than a slight influenza, was entertained clinically, and without an autopsy the death would have been attributed strictly to acidosis. Even when an autopsy proves negative, it is a question whether blood cultures may show an invasion by bacteria in the terminal stages of acidosis, and whether the failure of insulin in such terminal cases may sometimes be explained in this way.

5. Causes of Death:—Hypoglycemia, infection, and unknown toxic properties of insulin have been mentioned as possible causes of fatality in coma cases treated with insulin. The toxic action of the very high doses seemed to be distinctly suggested by case 1321, in which there was striking recovery from a state of profound weakness after insulin was omitted. Very quickly, however, the sugar which had apparently been stored as glycogen during the insulin administration came flooding back into the circulation, the acetone which had practically disappeared returned in large quantities, and a return of coma symptoms com-

pelled the use of increasing doses of insulin. It is not certain that this death was due strictly to either infection or acidosis, but other causes should not be assumed without more definite evidence. The most probable theory is that death in the unsuccessfully treated cases is generally due to irreversible injuries of protoplasm which result from the acidosis but are not removed by the clearing up of the acidosis. A fatal lowering of the plasma bicarbonate concentration does not suffice as a general explanation, because recoveries sometimes occur in cases in which this lowering has been extreme and death results in some cases in which the plasma bicarbonate has remained spontaneously at a higher level or has been artifically kept high by alkali dosage. Mere poisoning with acetone bodies has never been a plausible explanation of coma, the widely variable acetone figures in blood and urine being one objection. An attempt to overcome this difficulty by an assumption that the acetone concentration in the cells may be different from that in the blood runs counter to actual analyses of tissues for acetone, which according to our experience furnish no better explanation than the blood analyses. The best course is to acknowledge that the fundamental nature of diabetic coma is unknown, and for that reason nobody yet knows why some coma patients may show no benefit or only transitory improvement under insulin treatment, or may die even after carbohydrate utilization has been restored and acetone has nearly or entirely disappeared.

IV. Treatment of Infectious Complications.

1. Local Infections:—The eight cases treated with insulin in the Institute may be grouped as follows:

Gangrene was represented by five cases with one death. Patients 1244 and 1316 had small sluggish ulcers of the feet, inclined to be "perforating" in type. Patient No. 2165 underwent amputation of one leg below the knee for typical arteriosclerotic gangrene, the progress of which had not been halted by insulin. The healing in all these cases was no different from what we have regularly obtained with diet treatment alone, and insulin was chiefly of value in reducing sugar more rapidly and enabling higher nutrition to be maintained. Patient No. 200 was treated chiefly by diet, and though healing of gangrene after involvement

of bones and tendons in a toe is rare, the result cannot be positively attributed to the insulin.

Patient 1336 entered the Institute with gangrene of both feet, due specifically to diabetes and not to arteriosclerosis, because the circulation in both feet was excellent. Diet treatment probably could not have been effective, because the extent of infectious involvement and the poor strength gave little chance of controlling the sugar. Insulin was efficacious in proportion to the dosage used, but it was employed over-cautiously and the diet was also too lax for thorough arrest of glycosuria and hyperglycemia. The hope that insulin would show specific curative properties under these conditions was disappointed. Similar results were mentioned (section I, paragraph 3 above) in cases 1379 and 2159 which received inaccurate treatment outside the Institute. Not insulin in itself, therefore, but control of the sugar seems to be the most important requirement for healing.

Patient 356 had a middle ear and mastoid infection. The control of the sugar by insulin was not ideal, and neither was the resistance to the infection either before or after operation, but the outcome was successful. It is not certain whether this case, because of its severity and the complication present, could have been controlled by diet alone, but an extreme degree of undernutrition would certainly have been required.

Patients 1194 and 1335 make up four whom we have seen with deep intermuscular abscesses of the limbs. The two earlier patients had recognizable pulmonary tuberculosis; in No. 1194 it was suspected, but No. 1335 had nothing suggestive in the history or examination. Rapid and uneventful healing followed simple incision in the first two cases which were treated by diet alone, and in No. 1194 who received insulin with undernutrition. In No. 1335 it was thought that the results might be improved by using insulin so as to avoid undernutrition in a surgical case. The relief of pain and the healing of all the wounds were much slower than with undernutrition, even though the sugar was apparently under control. When the diet was reduced to an undernutrition level, and the insulin dosage correspondingly reduced, the better healing was noticed by the surgeon who was unaware of any change in the treatment.

2. *General Infections:*—Without trying to enumerate minor ailments such as colds, mention may be made of 9 more serious conditions, including 5 deaths; the other 4 patients are still alive.

General septicemia was the essential feature in two cases, originating in No. 1240 from a carbuncle and in No. 1285 from a phlebitis of the leg. Owing to the small insulin supply, the dosage was hopelessly inadequate in the former case. In the latter, insulin, being still scarce, was used only in moderation because of the impression that the sepsis was hopeless even apart from the diabetes.

Pulmonary tuberculosis was suspected in cases 526, 787 and 1277. Recovery from the symptomatic standpoint has been complete in the former two cases under careful insulin treatment, and with the transformed state of nutrition and strength there is strong reason to hope that these recoveries will be permanent. No. 1277 still had slight cough at discharge, and owing to his disregard of treatment a fatal result was expected, and this expectation was quickly fulfilled. Of the 3 cases of positive tuberculosis, No. 1283 ran a rapidly fatal course notwithstanding insulin treatment of the rather mild diabetes. No. 328 was under suspicion from the outset, but nothing positive developed during the long initial treatment by reduced diet. When the patient returned for insulin treatment, after having brought himself almost to coma by prolonged disregard of diet, cough and physical signs of bronchitis were present. These largely cleared up when the diabetic symptoms were controlled by insulin and diet, but have since returned and bacilli have recently appeared in the sputum. No. 1331 entered with moderately advanced pulmonary tuberculosis and a small empyema, and has improved to a remarkable extent. The abundant nutrition which is made possible by insulin offers the only hope for these last two cases, which would have been inevitably fatal under treatment by diet alone.

The fatal case No. 191 is ranked among the infections, though the exact cause of death was undetermined. It is certain that some acute intercurrent trouble was responsible for the fatality in a case in which the progress and prognosis had been excellent.

3. Insulin Dosage:—It is known from universal experience that infections lower the tolerance and create an increased tendency to glycosuria, hyperglycemia and acidosis. As the same fact holds under insulin treatment, infections generally require either an increase of the dose or a reduction of the diet. In cases beginning treatment, the requirement for high doses is illustrated by practically all the examples mentioned. It is least marked, how-

ever, with tuberculosis, and here perhaps secondary infections are the determining factor, since the tubercle bacillus itself seems to have less influence in lowering the tolerance than any other organism. The higher dosage is also often needed with small local infections, including dry gangrene, even though fever and all other systemic symptoms may be absent. The same rule is illustrated by cases which are running smoothly on a fixed program of dosage and diet, which sometimes must be radically changed to maintain sugar-freedom during an influenza or some other intercurrent infection. The degree of disturbance is by no means uniform, but may vary from slight to extreme in different cases. Theoretically, there may be two reasons for the increased requirement; either the function of the patient's islands may be impaired during infection, or the consumption of insulin by the body may be higher. Both possibilities might be correct. Insulin treatment opens the opportunity for direct evidence on the question. For example, if prolonged tests prove that a given patient possesses scarcely any internal pancreatic function of his own, and if a large increase above his regular insulin dosage is required to prevent glycosuria during an infection, there is a basis for the conclusion that the body is consuming more insulin. Precautions are necessary against the disturbing factor of acidosis. Undoubtedly the greatest increase of insulin requirement is found when the infection is attended by acidosis, and such an increase merely follows the usual rule for acidosis and does not necessarily prove anything concerning the specific infectious influence. There is as yet no basis for judgment whether the acidosis in such cases results solely from the impairment of carbohydrate utilization by the infection or whether it is to any extent produced primarily and directly by the infection.

4. Incidence of Infections:—There has been a widespread preconceived idea that extremely undernourished patients must be easy victims to infection, and that the benefit to their diabetes must be largely counterbalanced by an increased death rate from respiratory and other ailments. This opinion is supported by the universal experience with untreated diabetic cases and those in which the symptoms are partially controlled by inadequate or inaccurate measures. Repeated statements[6, 8, 16] have been made of our experience proving that for thoroughly treated cases this idea is not only untrue but is the direct opposite of the truth.

All diabetics have a more or less reduced resistance to tuberculosis, but the incidence of tuberculosis among them becomes lower in proportion to the thoroughness of the treatment, irrespective of the degree of undernutrition required for this purpose. We have never known of the development of a case of tuberculosis in a patient under strict treatment without suggestive indications that the infection originated prior to the treatment. Though the tuberculosis death rate was thus brought very low, as shown by Joslin and ourselves, there is every reason to hope that it will be reduced further with insulin, by reason of the higher nutrition which should be an important aid when the diabetes can be effectively controlled at the same time. A more important element is the prophylaxis resulting from the fact that many more diabetic cases will now be kept under therapeutic control than formerly.

The situation regarding ordinary respiratory, pyogenic and other infections is different. It cannot be too strongly emphasized that diabetics whose blood sugar has been kept normal, even at the price of the most extreme emaciation, have shown not merely normal but a higher than normal immunity to such infections. As stated heretofore, we have never seen a single infectious or other complication develop in such diabetics, to the extent of even a single boil or ulcer. Amputations for gangrene have uniformly been followed by better healing than might have been anticipated from the sclerosis of blood vessels, and no slough or failure of repair has ever occurred. Respiratory infections of the nature of colds or grippe have been rarer among the stringently undernourished diabetics than among the staff. During a typical influenza epidemic in a military hospital,[17] not a diabetic contracted the infection except one who broke diet and deserted and acquired it during his absence. Whether undernutrition raises resistance to certain bacterial invasions is unproved as a general law, but the facts regarding diabetic cases thoroughly controlled by reduced diets are established regardless of any theories or preconceived opinions.

With insulin treatment and the accompanying higher nutrition, we have been struck by the somewhat higher incidence of minor infections. When colds or influenza are prevalent, the patients contract it as frequently as the staff, though no oftener. The question of a specifically reduced resistance to pyogenic organisms in patients with hyperglycemia is suggested by several in-

decisive observations. Otitis media in the small child No. 918 at her home proved to be not serious, and may have been strictly accidental, though contrary to our former experience. Patient No. 3 has had the same trouble recently. Patient No. 396 was allowed a higher diet than usual, on account of the special circumstances in a rather mild case, and he had a frequently recurring slight staphylococcal infection of the nose, which was attributed to the hyperglycemia accompanying his liberal diet. Later, on a still higher diet with insulin, the same trouble was persistent, and again was probably connected with the slight continuous hyperglycemia. Recently the plasma sugar has been kept normal, and the infection has cleared up completely. A type of observation which will be conclusive if it can be frequently enough repeated is that mentioned in case 1335 above, where the draining abscess of the leg reacted sluggishly with liberal diet and insulin and seemed to heal much better when undernutrition and less insulin were used.

5. Methods of Treatment:—The above observations are merely suggestive, and the tentative deductions may prove erroneous. The poor resistance of diabetic patients is generally considered on a par with the absence of wound healing in totally depancreatized dogs. Banting and Best proved that their original pancreatic extracts enabled healing to occur in such dogs, and Bliss confirmed this fact with the purer Iletin of the Lilly Company. It is therefore to be anticipated theoretically that this and other forms of insulin should assist diabetic patients in resisting infection. It seems evident, however, that this help consists only in controlling the diabetes, not in any other specific property of the insulin. Therefore a fairly positive conclusion seems warranted that the resistance may often remain subnormal if the conditions of diet and dosage are such that the diabetes is only partially controlled. A physician is therefore not absolved from responsibility by the mere giving of insulin, unless certain conditions are fulfilled which sometimes are very difficult. The above mentioned observations regarding diet may be explained by one of two assumptions; either that undernutrition favors healing and resistance in general, or that control of all diabetic symptoms is achieved so much more easily and smoothly with the aid of undernutrition. It is to be feared that infections will

prove more troublesome among patients who are allowed to have hyperglycemia and glycosuria under insulin treatment.

Accordingly, for the present at least, we expect to use high nutrition in the presence of infection only for tuberculosis. With other infections, insulin is still a godsend, because it permits bringing the diabetes under control so much more rapidly and obviates the extreme grades of undernutrition. For small intercurrent ailments, however, we shall still reduce the diet, especially in fat, rather than depend merely on an increase of insulin dosage. The question is probably most important in connection with surgical infections and amputations. Here it has always been difficult to enforce the benefits of undernutrition, and surgeons will be strongly inclined to believe that one of the greatest blessings of insulin will be found in the ability to give their patients high diets before and after operations. Our policy, on the contrary, will be to use undernutrition in conjunction with insulin, partly for the sake of more efficient control of the diabetes in an emergency and partly because of the empirical benefits which seem to be real whether explained or not. This plan may be opposite to the practice of the majority, and only further experience can decide what is best.

6. General Considerations:—There can scarcely be a doubt that, when insulin becomes generally available, it will be used by the greater number of physicians and patients as a means for gaining higher weight, strength and comfort and a more pleasing diet while largely disregarding glycosuria. When dietary restriction was the only means of relief, the general profession did not master the means for keeping patients consistently sugar-free, and so-called diabetic specialists were not lacking who made no pretense of keeping symptoms under control in cases of any difficulty or severity. The striking improvement which will doubtless often be obtainable with insulin by careless methods will add to these tendencies. Furthermore, freedom from glycosuria involves the considerable inconvenience of an accurately weighed diet and constant supervision, while the opposite plan offers the possible chance of feeling well while eating with little or no restraint. An intermediate method is that of some specialists who employ careful diets but permit glycosuria in small amounts or at certain times of the day as a safeguard against hypoglycemia. It becomes necessary to inquire whether any

valid distinction can be drawn between much and little glycosuria, and if so, where the line between the harmful and the harmless quantities is to be drawn; and on the other hand, what justification there may be for the difficult undertaking advocated by the Toronto investigators and by ourselves, namely, that of keeping the urine normal and also the blood as nearly normal as possible. A defense may seem most difficult in two classes of patients, who really constitute the majority of all diabetics; first, in the very severe cases, where there is obviously little island function remaining and any possible loss of tolerance through downward progress could require only a small increase of insulin dosage to compensate for it; second, in mild cases past middle life, in which the symptoms and progressiveness are often slight and may be expected to become still slighter with the use of insulin. Under such circumstances, has strict treatment sufficient practical value to be worth while?

It must be confessed that a positive answer can be given only by time; but as human life and health on a wide scale are involved, some theoretical considerations favoring a careful policy may be worth mentioning. Biologically, the loading of the urine and blood with sugar is decidedly abnormal, and those who hope that such an abnormality may continue for many years without harm are at least taking serious risks. Medically, it must be considered that glycosuria represents active diabetes even when the patient takes sufficient insulin to feel well. The resulting condition seems to be no different from the mild and symptomless forms of diabetes which have long been known, as illustrated, for example, by case 1240. This patient was able to be strong and well while ignoring his diabetes. As he had been obese as well as diabetic for years, it is evident that his pancreatic islands kept him supplied with hormone for maintaining his nutrition, as efficiently as if insulin injections had been given with a similar disregard of glycosuria. Trouble came only with one of the infectious complications, to which these seemingly benign forms of diabetes are known to predispose, and a few days completed the transition from apparent health to death. Case 1285 is another good example without treatment, and case 1336 with partial treatment. It is questionable whether in any of these the rapidly spreading sepsis, once started, could have been stopped by any quantities of insulin. Those who assume that full doses of insulin might save such a patient are at least confessing that

thorough treatment is desirable in an emergency; and if such treatment is curative at such times, it is hard to see why it should not be advantageous all the time for prevention. We have gained the impression that the highest mortality from diabetes heretofore has occurred among the milder cases. The rapid progress and early death of unchecked severe cases in the young are the most impressive, but the number of such cases is comparatively small. The neglected mild cases in later life are much more numerous. The deaths may occur from well known complications such as carbuncle and gangrene, or from other infections which may dominate the picture so that diabetes is not even mentioned in the death certificate. Furthermore, the lowered resistance to infection is probably only one manifestation of the impaired vitality and reparative power of the tissues against all kinds of injuries. An advanced form of sclerosis of the arteries supplying the feet is the usual basis of dry gangrene, which is rare in non-diabetics, while all degrees of arteriosclerosis are significantly common among elderly untreated diabetics. Though diabetes sometimes runs a remarkably long and benign course, the more carefully observations are made the more doubtful it becomes that any such patient actually escapes premature death or organic impairments, while the injuries in the great majority of cases are too evident to admit of any question. Moreover, both the infectious and degenerative complications occur not only in untreated cases but also in those which are partially treated so as to keep the sugar excretion within moderate limits. Theoretically, lax treatment with insulin would appear to mean nothing but the conversion of a given case into a milder but still active form of diabetes, and it seems plausible that such patients will remain exposed to all the infectious and other complications to which mildly diabetic patients have always been subject, when either heavy or slight glycosuria or sometimes only hyperglycemia has been permitted. If glycosuria can be entirely or partially ignored, it will be difficult to justify the further existence of diabetic specialists, since any intelligent physician can obtain equal results under these conditions. The question may be decided largely by the incidence and mortality of complications under the different methods; and if the different workers will collect and publish strictly objective figures without bias in favor of their own procedures, some trustworthy decision should be possible within the next few years.

V. Gain or Loss of Tolerance under Insulin Treatment.

The expectations from insulin treatment must be governed largely by whatever conceptions are held concerning the nature of diabetes. One of the welcome features of the discovery of insulin is the aid which it will bring to investigation as opposed to mere opinion in this field; in other words, the light which it will throw upon the question whether the progressiveness of diabetes is the natural and inevitable consequence of some mysterious dyscrasia, according to prevalent medical tradition, or whether it is due entirely to two definite and demonstrable forms of injury, namely, those from functional overstrain and from infections, as indicated by considerable scientific evidence which has not been generally accepted. The facts now favoring the latter view may be outlined in historical sequence as follows.

1. All the early diet treatments were planned with more or less vague ideas of sparing one or another defective function, but Naunyn may be credited with the first definite statement that diabetes represents a weak metabolic function which may be broken down by overstrain and built up to some extent by rest, and that all diabetic cases should be kept sugar-free if possible for this reason.

2. The evidence that the seat of this deficient function is entirely in the pancreatic islands, and that diabetes results solely from disease of these islands, need not be reviewed here. The proof has been completed by the discovery of insulin, which disposes of the widespread medical skepticism on this point.

3. The strongest objection to the island theory has been the inability of pathologists to discover extensive or progressive lesions in most cases. The pancreatitis generally found does not explain the progressiveness, for often it is found most marked in the relatively mild and unprogressive diabetes of later life and trivial or quiescent in the rapidly fatal youthful cases.

4. Scarcity of islands has been an almost invariable finding in genuinely severe cases of diabetes, but the degree of disappearance has borne no relation to the extent of the visible fibrous or inflammatory changes. Weichselbaum discovered and described hydropic degeneration as a specific diabetic lesion of the islands, but ranked it among the etiologic changes, on a par with "atrophy" and hyalin degeneration.

5. A precise reproduction of human diabetes, in respect to glycosuria, acidosis, lipemia, progressiveness and all other clinical details can be obtained in dogs by partial pancreatectomy. When the pancreas remnant is larger, diabetes can still be produced by setting up acute inflammation in it, and may progress to a fatal end after subsidence of the inflammation has left behind only slight fibrosis or an actually normal appearance of the pancreatic parenchyma. These facts and a suggestive series of clinical observations have supported the theory that a large proportion of diabetic cases, particularly in young persons, originate in acute pancreatitis, of which only some healed scars and sometimes no traces at all remain at autopsy.[18]

6. The pathological change which accompanies downward progress and which ultimately leads to complete disappearance of the beta cells of the islands in experimental animals is hydropic degeneration. This can be induced and halted at will by suitable feeding, and thus can be demonstrated positively as an anatomic breakdown of island cells due to functional overstrain.[18]

7. Further studies of the pancreas in human cases have proved that hydropic degeneration never occurs in the absence of diabetes, and is always present with diabetes when there has been sufficiently intense functional overstrain for a sufficient length of time, provided any functioning island tissue still remains. Thus, more or less vacuolation is revealed by sufficiently thorough search in the great majority of coma cases and in most severe and progressive cases uncontrolled by treatment. When the progressiveness is less marked or has been more or less arrested by treatment, visible vacuolation is slight or absent. The facts could not be otherwise, since this process represents a very rapid breakdown of cells by functional exhaustion, which could not possibly continue throughout the years of duration of a mild diabetic case. With very slow progressiveness, however, it is assumed that the same process goes on in a correspondingly slow manner, which must usually escape microscopic demonstration. The loss of islands in human cases is thus reduced to exactly the same basis as in dogs; first, the destruction of some of them and injuries of the remainder by inflammation; second, the further breakdown of cells and whole islands through functional overstrain.[18]

8. The progressiveness of human cases under strict diet previously has been readily explained by the focusing of attention exclusively upon carbohydrate. Appreciation of the relation of the island function to total metabolism and the dominant requirement of undernutrition in treatment is prerequisite to the understanding of the pathological process. As shown in papers 2 and 3, the discovery of insulin has not altered these facts but has made them easier to demonstrate.

9. The progressiveness of human diabetes, including the types and ages which have always carried the worst prognosis, can be reduced nearly or completely to the vanishing point by sufficiently strict avoidance of the injuries from functional overstrain and infections.[7, 8, 9] We believe that the best clinical results are obtained by treatment on this principle, as indicated by our general statistics in a series of cases of unusually high average severity. The figures are not intended, however, for invidious comparison with those of others, as exact comparisons of severity are difficult, and it might even be possible that less stringent measures would be more favorable in a general practical sense by occasioning fewer departures from diet. From the theoretical viewpoint, it must be recognized that few patients escape intercurrent infections altogether, and an occasional cold or diarrhea may depress the tolerance perceptibly. Furthermore the diet is not conducted like that of a dog in a cage, where the sole consideration is the accurate proof of a principle. At home some mistakes and accidents nearly always arise, and even in an institution the comfort of the patient always demands a diet at the upper limit of his tolerance. This is equivalent to the constant running of a damaged machine at its utmost capacity, and from purely mechanical reasoning breakdown or wearing out is to be expected. The severest cases present the difficult situation that the patient can easily slip downward from trivial causes and is practically unable to recover the lost ground. Even against these disadvantages, we performed the experiment of taking a number of very severe cases and demonstrating the arrest of their former progressiveness during several years of continuous residence in this Institute under stricter control than is usually possible at home (cases 24, 54, 85, 839, 878, etc.). Examples of non-progressiveness under accurate home treatment have been described elsewhere and are also shown in the present series

though the same cases sometimes demonstrated their progressiveness with excessive diets or infections (Nos. 2, 3, 174, 191, 337, 529, 539, 574, 783, 1016, etc.).

Apparent exceptions are generally explainable. We do not interpret Williams' statements[19] as meaning that all his patients were uninterruptedly free from hyperglycosuria and glycosuria under all conditions and at all times of day. The downward progress mentioned by Banting, Campbell and Fletcher[2] in one of our patients (E. H.) was real, but it should be added that this patient had been subject to numerous slight throat infections and to peculiar diarrheal attacks which affected her tolerance markedly, and furthermore had been away from observation for a year or more at a stretch and during these times had often had hyperglycemia and occasionally glycosuria. Our position on this subject is supported not only by our own experience but by the general fact that the progressiveness of diabetes has become less and the lives of patients have been lengthened in proportion as the treatment of diabetes has been improved. Diabetic dogs, with no inherently progressive tendencies, progress downward and die if placed under the conditions to which most human patients are still subjected for the sake of their comfort. The elimination of known harmful influences to the greatest practicable extent reduces the progressiveness of human cases so near to zero that any unknown element of spontaneous progressiveness appears to be excluded.

10. The concept of "functional overstrain of islands" has naturally appeared vague and hypothetical to most persons heretofore. It is now possible to give it a quantitative mathematical expression, by reckoning the insulin dosage required to compensate for the downward progress which a patient has suffered by departure from diet, as illustrated in several cases of this series (Nos. 70, 787, 1020, 1083, 1238, etc.).

11. The injurious influence of infections can now also be estimated in terms of insulin dosage, as mentioned under Section IV.

12. Diabetic dogs show decline of tolerance and degeneration of islands from continuous hyperglycemia without glycosuria, and our experience indicates the same occurrences in human cases of the severe type. If glycosuria is admitted to be injurious, we have been unable to see any reasons why hyperglycemia

of 0.3 per cent. or over should not be injurious even if renal impermeability happens to prevent sugar excretion, or why the warning given by a rising blood sugar level should not be heeded as a means of preventing glycosuria. All writers who have ignored hyperglycemia in their treatment have found their severe cases of diabetes to be usually progressive, and though they have evaded responsibility by the arbitrary assumption of a mysterious inherent tendency, it would appear to be a difficult matter for them now to deny that an abnormal functional state is represented by the abnormal level of blood sugar. Now it has become possible to measure the difference between hyperglycemia and normal blood sugar in terms of insulin, and to show that the extra burden placed upon the pancreatic islands by an elevated blood sugar level may amount to a very appreciable fraction of their probable functional capacity (Cases 339, 783, 839, 918, 989, 1020, 1172, 1304, 2165, 2166).

13. Some confusion has been created by the relative absence of progressiveness of some cases, especially those in later life, even with marked and continuous hyperglycemia. As the same differences in progressiveness are found when glycosuria is permitted, some patients excreting much sugar without apparent harm for years, no argument is thus furnished to those who base their treatment upon the avoidance of glycosuria alone. An additional fact is that the food tolerance is fairly high in many of these benign cases when hyperglycemia is allowed, but, especially when the diabetes is of many years' standing, reduction of the blood sugar to normal may be difficult or almost impossible by the most extreme privations in diet. Our past policy has been to keep the plasma sugar in such cases only within such moderate bounds as seemed necessary for a safeguard against complications. Such patients in fact commonly have arteriosclerosis and are the most frequent candidates for other complications when untreated. If it can be assumed that certain forms of pancreatic injury involve a reduced sensitiveness of the islands to functional stimuli, all the above phenomena receive a simple explanation. Though this is a pure assumption, it may be useful as showing that the problem is by no means hopeless. In former writings we have as far as possible avoided speculation, which has been so mischievous as a substitute for investigation in diabetes; but now

that the general theory is apparently becoming better established, a few supplementary hypotheses may be permissible.

14. Studies in diabetic dogs made it doubtful that the blood sugar itself is the direct stimulus to the function of the islands. As the function continues efficiently when nervous control is excluded,[20] it was suggested that the humoral regulation may possibly be exercised through the actual concentration of the hormone in the blood stream, by a kind of mass action. The blood sugar has been used as a therapeutic guide because it is more delicate and reliable than any other known, but it is not necessarily infallible under all conditions. For example, when considerable quantities of insulin are received by injection from the outside, distinctly novel conditions are created. The possibilities concerning the concentration in the blood, the functional relief or even storage of hormone in the islands during the temporary plethora following injections, and various unknown factors may be very different from the conditions when the patient's own pancreas is the sole source of supply. Accordingly, it cannot be predicted dogmatically that either hyperglycemia or glycosuria will cause injury or downward progress under these new circumstances. We strongly favor Banting's advice that both urine and blood be kept as nearly normal as possible, on general theoretical grounds and on the incomplete evidence already mentioned. The experience thus far gives the distinct impression that if decline of tolerance results from glycosuria and hyperglycemia under insulin treatment, it is at least decidedly less marked and rapid than under similar conditions without insulin. Only time and further observations can decide this point.

15. The observations concerning progress in our series of cases to date are given in the individual histories. In three instances (Nos. 823, 839 and 1167) there seem to be fairly plain indications of a decline of tolerance with glycosuria notwithstanding insulin treatment. It would thus appear that insulin does not confer any absolute immunity against downward progress. Our experience as a whole, however, gives the distinct impression that the loss of tolerance resulting from glycosuria or hyperglycemia in cases treated with insulin is at least decidedly less marked and rapid than under similar conditions without insulin. Reasons may possibly be found in some of the hypothetical considerations

in the preceding paragraph, or merely in the more limited quantities of sugar present when insulin is used. The hope for an opposite direction of progress, namely, for increase of the patient's tolerance, must rest upon the possibility that insulin may reduce the demands upon the patient's islands more powerfully and effectively than any mere restriction of diet. Actual gain in assimilative power, beyond anything achieved by dietary measures alone, seems to have occurred in some cases, for example Nos. 24, 989, 1020, 1034, 1214, 2127 and 1305. Against the chance of actual cure stands the probability that the islands in practically all established cases have been damaged or exhausted in their regenerative as well as in their functional capacity. As previously mentioned, thorough insulin treatment with a view to favoring a cure as far as possible has been attempted in all mild or incipient cases, especially in children, in whom the pancreas should increase greatly in size with advancing years (Nos. 274, 339, 1156, 1255, 1295, 1306, 1333, 1346, 2228, 2230); but the results cannot yet be judged. Irregularities of the insulin requirement have sometimes been noticed in certain cases, and in particular the benefit of a preceding course of insulin may persist for a longer or shorter time after the injections are discontinued. Storage of insulin or functional recuperation by the islands are conceivable explanations. As noted elsewhere, gain of weight ordinarily increases the need for insulin, if other factors remain constant. On the whole, with these allowances for known and unknown influences, our experience is that the insulin requirement in a given case usually shows little tendency to change, and when insulin is withdrawn the patient ordinarily lapses quickly back to approximately his former condition. Though such results are discouraging to hopes of cure in most cases, they are to an equal extent encouraging for the prevention of downward progress. It is scarcely conceivable that an extract containing the hormone of the islands can have any action except through substituting for the function of the islands. The arrest of downward progress by this means is clearly explainable under the theory here outlined. If on the other hand there is some mysterious cause of progressiveness apart from functional overstrain, this should naturally continue to manifest itself. The believers in such a constitutional or organic dyscrasia must naturally expect the deterioration to continue until all severe cases are reduced to the level of "total" diabetes and their entire

insulin supply must be received by injection. The absence of any increased insulin requirement in all carefully treated patients to date furnishes strong support to the doctrine that the essential cause of progressiveness in diabetes (apart from chance infections) consists solely in functional overstrain of the pancreatic islands. The insulin treatment enables the necessary functional rest to be obtained much more easily and at much less sacrifice of nutrition than before. It therefore provides the means for a more conclusive test of this theory and for its wider acceptance in case the arrest of progressiveness observed up to the present is found to continue in the future.

Summary and Conclusions.

1. All of the 79 cases of uncomplicated diabetes in this series have responded favorably to treatment with insulin. There has been only one death, due to flagrant disregard of diet. The increases of diet, weight and strength made possible by the new treatment even in the severest cases are beyond comparison with anything possible under any other known method.

2. Of 9 coma patients treated with insulin, 5 died and 4 recovered. All or nearly all of these cases were evidently hopeless with ordinary treatment, and the saving of lives can be directly credited to the insulin. In most of the unsuccessful cases insulin reduced or abolished glycosuria and ketosis, and the reasons for death under these circumstances are still hypothetical. The necessary dosage in coma cases may run into hundreds of units in 24 hours, the possible limits of safety or usefulness being as yet undetermined. All the measures formerly in use, together with somewhat more glucose or carbohydrate than formerly customary, should be used as adjuvants to insulin.

3. Among 14 cases complicated by local or general infections, there have been 5 deaths and 9 survivals. The higher nutritive level made possible by insulin promises to be especially important for cases of diabetes with tuberculosis. For other medical and surgical infections, notably gangrene, insulin is extremely helpful for bringing glycosuria and other symptoms under control more rapidly and thoroughly than otherwise possible while obviating the necessity of extreme undernutrition. The limited experience seems to indicate that moderate undernutrition is still beneficial

to such cases in conjunction with insulin, at least during the period of chief danger. Emphasis should be placed upon thorough control of the diabetes rather than upon high nutrition. The general resistance and the healing of wounds are no better under insulin than they have been under efficient dietary control heretofore. The incidence of respiratory and other minor infections is perhaps slightly higher than under the former strict undernutrition treatment. The lowering of tolerance which has long been familiar under diet treatment is now represented by an increase of the insulin requirement during infections.

4. We have followed the general principle that treatment should keep the urine normal and the blood as nearly normal as possible. It is seldom feasible with the present methods of using insulin to keep the blood sugar as rigidly normal as with diet alone, especially in severe cases, because of the danger of hypoglycemia, but with care this ideal can be rather closely approximated. All our attempts with lax or inaccurate diets in conjunction with insulin treatment have led to disastrous results. Thorough training regarding the use of both diet and insulin should be given, preferably in an institution, to all patients before they attempt the management of their condition away from direct supervision. After such training patients have proved able to continue the treatment successfully at home, and the average standard of fidelity has been higher than before. *Insulin has tremendously improved diabetic treatment, but has not simplified it.*

5. The occurrence, symptoms and treatment of hypoglycemia, as described by the Toronto investigators, have been confirmed. The avoidance of danger from this cause is ordinarily a simple matter both in an institution and for well trained patients in their homes.

6. Our general standards of nutrition have been, for growing children ample diets for their development, and for adults enough to keep them a few pounds below their original or normal weight and to make them comfortable and fit to work. While gross excesses of carbohydrate are avoided, the diets are nevertheless of agreeable mixed character, and are planned not in conformity with any fixed rule but rather to suit the empirical needs of each individual case in respect to both composition and total caloric value.

7. The insulin dosage necessary for control of symptoms under the above conditions has ranged between the extremes of 4 units and 70 units per day in different cases. The requirements vary with the severity, the total diet, the body weight, and other known and unknown factors. Our dosage also has been individualized to suit each case, as we believe that all rules based on the glucose value of the diet or any other principle yet known are widely fallacious.

8. Exercise seemed to accomplish an increased utilization of sugar in three cases under insulin treatment, as formerly known under diet treatment. The influence in this direction is only slight, and the chief practical importance of the observations lies in the warning that heavy exertion may increase the danger of hypoglycemia in certain cases.

9. Insulin showed no perceptible influence upon non-diabetic conditions such as kidney disease, cirrhosis of the liver, or neurasthenia.

10. In 3 cases, diabetics seemed to lose tolerance demonstrably when glycosuria was permitted with insulin treatment. Several other patients have shown gain of assimilative power with insulin beyond anything that could be expected with diet alone. There seems to be no chance of real cure unless possibly in certain mild or incipient cases, with which the trials are still in progress. On the whole, when allowance is made for accidental or modifying factors, the insulin requirement of most cases remains fairly constant and the patients return to their former condition if insulin is withdrawn. These observations at least encourage the hope that downward progress can be arrested by suitable use of insulin, and they therefore add support to the theory that functional overstrain is the essential cause of the progressiveness of diabetes.

From a practical standpoint, three points seem worthy of emphasis by repetition. *It is feasible for patients at their homes to remain free from glycosuria and nearly free from hyperglycemia under combined treatment by diet and insulin. Overnutrition makes freedom from glycosuria difficult, and exposes to acidosis, infection and other dangers. Insulin is a literally epoch-making discovery, which revolutionizes the results of diabetic treatment when properly employed, but it cannot atone for lax or inaccurate dietary methods.*

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